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(54) Title: BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF HEPARIN-BINDING PROTEIN (HBP)

(57) Abstract: The present invention relates to providing new peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said fragments for the manufacture of a medicament for the treatment of Gram positive and/or Gram negative infections. Thus, the peptides of the inventions can be used for treatment of pneumonia and meningitis. The peptides of the invention may also be advantageously used for the treatment of any pathological condition demanding modulating of inflammatory response and/or a condition involving sepsis and/or, disseminated intravascular coagulation. Among other pathological conditions, which may be regarded for the treatment with the peptides of the invention, are conditions involving cell apoptosis.



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**Bactericidal, anti-apoptotic, pro-inflammatory and anti-inflammatory peptides
of heparin-binding protein (HBP)**

5 Technical field of the invention

The present invention relates to providing peptides derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said peptides for the manufacture of a medicament for the treatment of Gram positive
10 and/or Gram negative infections, sepsis, disseminated intravascular coagulation, modulation of inflammatory response, and/or prevention of cell apoptosis.

Background of the invention

15 A local infection or injury in any tissue rapidly attracts white blood cells into the affected region as part of the inflammatory response, which helps fight the infection or heal the wound. The inflammatory response is complex and is mediated by a variety of signalling molecules produced locally by different types of cells. Some of these molecules act on nearby capillaries, causing the endothelial cells to adhere
20 less tightly to one another but making their surfaces adhesive to passing white blood cells. Other molecules act as chemoattractants for specific types of blood cells, such as monocytes, causing these cells to become polarised and crawl toward the source of the attractant.

25 White blood cells, specifically polymorphonuclear leukocytes (PMNs), produce a large variety of peptides involved in the inflammatory response. Among these peptides is the heparin-binding protein (HBP), which was first isolated from azurophile granules of human PMNs. A highly homologous peptide was also isolated from PMNs of porcine origin and has been named porcine heparin-binding
30 protein (pHBP) (Flodgaard et al., 1991, Eur. J. Biochem. 197: 535-547; Pohl et al., 1990, FEBS Lett. 272: 200 ff.) HBP has otherwise been termed CAP37 (WO 91/00907, US 5,458,874 and 5,484,885) and azurocidin (Wilde et al. 1990, J. Biol. Chem. 265:2038-41).

35 Sequence analysis of HBP has revealed that the protein bears many similarities to serine proteases, which are important in inflammatory processes, e. g. neutrophil

elastase (47% homology) or protease 3 (43% homology), however HBP lacks protease activity due to mutations of two of three amino acids in the highly conserved catalytic triad. The structure of HBP appears from WO 89/08666 and Flodgaard et al., 1991 (Eur. J. Biochem. 197: 535-547).

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HBP was originally studied because of its antibiotic and lipopolysaccharide binding properties (Gabay et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:5610-5614 and Pereira et al., 1993, Proc. Natl. Acad. Sci. USA 90: 4733-7). However, a number of experimental evidence now supports the concept that HBP is a multifunctional protein, and, in addition to its bactericidal role, is involved during the progression of inflammation due to its effect on the recruitment and activation of monocytes (Pereira et al., 1990, J. Clin. Invest. 85:1468-1476, and Rasmussen et al., 1996, FEBS Lett. 390:109-112), recruitment of T cells (Chertov et al., 1996, J. Biol. Chem. 271:2935-2940), as well as on the induced contraction of endothelial cells and fibroblasts (Ostergaard and Flodgaard, 1992, J. Leuk. Biol. 51:316-323). Ostergaard and Flodgaard (op. cit.) also disclose increased survival of monocytes treated with HBP. Furthermore, in animal models of fecal peritonitis, HBP treatment has been shown to rescue mice from an otherwise lethal injury (Mercer-Jones et al., 1996, In: Surgical Forum, pp. 105-108; Wickel et al., 1997, In: 4th International Congress on the Immune Consequences of Trauma, Chock and Sepsis, Munich, Germany, pp. 413-416).

Using synthetic peptides derived from the sequence of human HBP in laboratory and preclinical research some functions of the protein has been structurally localised within the molecule of HBP. Thus, it has been shown that, for example, a high Gram negative bactericidal activity of human HBP is most probably associated with residues 20-44 of the human HBP amino acid sequence (Pereira et al., 1993, Proc. Natl. Acad. Sci. USA 90: 4733-7 and US 6,107,460). The amino acid residues 95-122 of the human HBP sequence have been associated with a capacity of the protein to stimulate protein kinase C in vascular endothelial cells (Pereira et al., 1996, J. Leukoc. Biol. 60:415-22).

30

It would be advantageous to produce new peptides derived from the sequence of human HBP, porcine HBP, or analogues of these sequences, such as, for example, neutrophil elastase, to use for the manufacture of new bactericidal, anti-apoptotic

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medicaments and medicaments for modulation of an inflammatory response, especially the inflammatory response to bacterial infection.

Summary of the invention

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Thus, in one embodiment the present invention relates to providing peptides having a peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula

10 $X^1-X^2-Cys-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-Cys-X^{18}-X^{19},$

wherein

the side chains of the two Cys residues are connected via a disulfide bond,

wherein

15 X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser,

Group 2 consisting of Arg and Lys,

Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,

Group 4 consisting of Asn and Gln, or

20 Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

wherein

X^1 can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;

25 X^2 is selected from Group 5 or Group 3;

X^3 , X^{15} and X^4 are selected from Group 1;

X^5 is Thr or selected from Group 1;

X^6 , X^{11} , X^{12} , X^{13} and X^7 are selected from Group 3;

X^8 and X^{17} are selected from Group 1, 3 or 4;

30 X^9 is selected from Group 5, 1 or 3;

X^{10} is selected from Group 2, 3 or 4;

X^{14} is Ser or selected from Group 3;

X^{16} and X^{18} is selected from Group 1 or 3

35 X^{19} can be represented by a sequence consisting of 2-5 amino acid residues or a single amino acid residue selected from Group 5, 2, or 4,

with the proviso, that when X¹ includes Pro, then X¹⁹ is Gln.

5 The invention concerns providing peptides derived from the sequence of human HBP (hHBP) and/or porcine HBP (pHBP) and/or human neutrophil elastase capable of proinflammatory or anti-inflammatory activity, bactericidal and/or monocyte attractive activity, and/or capable of preventing cell apoptosis.

10 Further, the present invention discloses a recombinant process for the production of the above peptides, and the use of the peptides of the invention for the manufacture of a medicament for prevention or treatment of Gram negative and/or Gram positive bacterial infections, sepsis, severe sepsis, septic shock, disseminated and/or intravascular coagulation, stimulation or inhibition of the inflammatory response, or cell apoptosis.

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Figures

Figure 1 depicts IL-6 secretion induced by HBP peptides in the absence of bacterial components.

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Figure 2 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion

Figure 3 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion in the presence of PGN.

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Figure 4 shows the effect of HBP 20-44 peptides on LPS induced IL-6 secretion in the presence of PCW.

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Figure 5 shows the effect of N-Ac, C-amido hHBP 20-44 on PGN induced IL-6 secretion.

Figure 6 shows the effect of R34Q pHBP 20-44 on PGN induced IL-6 secretion.

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Figure 7 shows the effect of different substitutions in the sequence of hHBP and pHBP on production of IL-6 induced by LPS.

Figure 8 shows the effect of different substitutions in the sequence of hHBP and p HBP on production of IL-6 induced by PGN.

5 Table 1 shows the potential applications for mono-functional peptides of the invention.

Detailed description of the invention

10 Inflammation

The present invention relates to providing peptides and using said peptides for the manufacture of a medicament for modulation of the inflammatory response.

15 Inflammation is a defence reaction caused by tissue damage due to a mechanical injury or bacterial, virus or other organism infection. The inflammatory response involves three major stages: first, dilation of capillaries to increase blood flow; second, microvascular structural changes and escape of plasma proteins from the blood-stream; and third, leukocyte transmigration through endothelium and accumulation
20 at the site of injury and infection. The inflammatory response begins with a release of inflammatory mediators. Inflammatory mediators are soluble, diffusible molecules that act locally at the site of tissue damage and infection, and at more distant sites, influencing consequent events of the inflammatory response. Inflammatory mediators can be exogenous, e. g. bacterial products or toxins, or endogenous, which are
25 produced within the immune system itself, as well as injured tissue cells, lymphocytes, mast cells and blood proteins.

In one aspect the present invention relates to the inflammatory response to bacterial infection.

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By "bacterial infection" in the present context is meant the invasion of normally sterile host tissue by bacteria. Bacterial infection of the invention may be due to invasion of either Gram negative or Gram positive bacteria, or a combination thereof or other infectious agents including fungi and virus. In one embodiment the present invention
35 relates to the inflammatory response due invasion of Gram negative bacteria se-

lected from the group comprising Acetobacteriaceae, Alcaligenaceae, Bacteroidaceae, Chromatiaceae, Enterobacteriaceae, Legionellaceae, Neisseriaceae, Nitrobacteriaceae, Pseudomonadaceae, Rhizobiaceae, Rickettsiaceae, Spirochaetaceae, Vibrionaceae, Brucella, Chromobacterium

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In another embodiment the invention relates to the inflammatory response due to invasion by Gram positive bacteria selected from the group comprising Bacillaceae, Micrococcaceae (for example *Staphylococcus aureus*), Mycobacteriaceae (for example *Staphylococcus pneumoniae*), Peptococcaceae.

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In an additional another embodiment the invention relates to the inflammatory response associated with sepsis, severe sepsis and/or septic shock.

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By "sepsis" in the present context is meant the systematic inflammatory response to bacterial infection, characterised by one or more of the following conditions as a result of infection: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ torr (<4.3 kPa), and WBC $>12\,000$ cells/ mm^3 or <4000 cells/ mm^3 or 10% immature (band) forms.

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By "severe sepsis" in the present context is meant sepsis associated with organ dysfunction, hypoperfusion, or hypotension, hypoperfusion and hypotension abnormalities may include, but are not limited to, lactic acidosis (acidic condition in blood), oliguria (meaning reduction in urine production), or acute alteration in mental status.

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By "septic shock" in the present context is meant sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.

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In yet another embodiment the invention relates to the inflammatory response associated with disseminated intravascular coagulation (DIC).

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By "DIC" in the present context is meant a pathophysiologic condition involving a continuum of events that occur in the coagulation pathway in association with a variety of well-defined clinical situations, including sepsis, major trauma, and abruptio placenta, and with laboratory evidence of the following: procoagulant activation, fi-

brinolytic activation, inhibitor consumption and biochemical evidence of end-organ damage or failure.

Proinflammatory peptides

It is an objective of the present invention to provide new peptides, which are capable to serve as additional mediators of the inflammatory response, the so-called pro-inflammatory peptides are particularly useful but not limited to patients selected from groups of immune-suppressed patients, cancer patients, patients with autoimmune diseases and patients undergoing major surgery.

In the present context by the term " pro-inflammatory peptide" is meant an artificial peptide compound which is capable of

- i) Stimulating, either alone or in synergistic action with bacterial products including, but not limited to LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyldipeptide) and PCW (purified cell wall from bacteria), the gene expression in the immune cells, preferably monocytes/macrophages, leading to secretion of endogenous inflammatory mediators including receptors for inflammatory mediators and transcription factors involved in the signal transduction of the inflammatory mediators, said mediators being preferably selected from the group comprising cytokines, selected from the group TNFalpha, IL-1, IL-6, G-CSF, GM-CSF, M-CSF. Chemokines selected from the group comprising IL-8, MCP-1, receptors selected from the group Tissue factor and IL-2Ralpha. and/or
- ii) activating the production of bradykinin by the phase contact system, and/or;
- iii) serving as an attractant for monocytes, and/or
- iv) increasing the life-time of monocytes, neutrophils and other immune cells serving as an inhibitor of apoptosis, and/or
- v) activating vascular endothelial cells to express the adhesion molecules, said adhesion molecules being preferably selected from the group comprising PECAM, ICAM-1, E-selectins, VCAM-1, and/or
- vi) activate the contact phase system to produce bradykinin leading to an increased vascular permeability, and/or
- vii) increase the phagocytic potential of monocytes/macrophages, and/or
- viii) upregulate class-II MHC.

In one embodiment the pro-inflammatory peptide of the invention is a peptide

- i) derived from any of the sequences set forth in SEQ ID NO: 1, SEQ ID NO:588, or SEQ ID NO: 589,
- 5 ii) comprising one or more of the sequences set forth in SEQ ID NO: 2-587,
- 10 iii) capable of at least one of the above activities (i-viii) of an pro-inflammatory compound, more preferable at least two of the above activities, even more preferable at least three of the above activities, even more preferable at least four of the above activities, even more preferable at least five of the above activities, even more preferable at least six of the above activities, even more preferable at least seven of the above activities, and most preferably eight of the above activities.

15 In the present context the term "synergistic action" refers to the situation where the combined action of a bacterial product and a peptide of the present invention is a stronger pro-inflammatory stimulant than the pro-inflammatory stimulant a bacterial product or the present peptide, respectively would be on their own.

20 In another embodiment the invention provides a pro-inflammatory peptide capable of stimulating either alone or in synergistic action with bacterial products including, but not limited to LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyl dipeptide) and PCW (purified cell wall from bacteria) the secretion of cytokine IL-6 from monocytes, comprising two or more sequences set forth in SEQ ID NOS: 15-36, wherein said sequences constitute a contiguous
25 sequence derived from the sequence of hHBP set forth in SEQ ID NO:1. Further, the pro-inflammatory peptide may be used for the manufacture of a medicament for the treatment of individuals having suppressed immune system, cancer, auto-immune diseases and/or trauma.

30 In a preferred embodiment the invention concerns an pro-inflammatory peptide, wherein said peptide has the sequence NQGRHFCCGALIHARFVMTAASCFQ (SEQ ID NO: 594). Even more preferred the peptide, wherein the sequence identified in SEQ ID NO: 594 has the N-terminal and C-terminal modified, as for example the N-terminal amino group being amidated and the C-terminal carboxy group being acetylated.

Anti-inflammatory peptides

It is another important objective of the invention to provide new anti-inflammatory peptide, which are capable of serving as inhibitors of the sustained inflammatory response.

The continuous presence of inflammatory mediators, such as for example TNF alpha in the body in response to sustained presence of bacterial products or even live bacteria locally during days or weeks following trauma and/or infection promotes the reactions to inflammation, such as, for example, heat, swelling, and pain. The sustained inflammatory response has been proven to be very harmful to the body. If the bacterial products or live bacteria become spread universally in the body from their local focus the inflammatory reaction becomes overwhelming and out of control and leads to sepsis which eventually progress further to severe sepsis and septic shock. Anti-inflammatory peptides may be used to block or suppress the overwhelming sustained inflammatory response represented by a massive and harmful cytokine cascade in the blood and vital organs such as lung, liver intestine, brain and kidneys.

In the present context by the term "anti-inflammatory compound" is meant a compound which is capable of

- i) decreasing or inhibiting the gene expression in the immune cells, preferably monocytes/macrophages in response to bacterial products, live bacteria or trauma to produce endogenous inflammatory mediators including receptors for inflammatory mediators and transcription factors involved in the signal transduction of the inflammatory mediators, said mediators being preferably selected from the group comprising cytokines, selected from the group TNFalpha IL-1, IL-6, G-CSF, GM-CSF, M-CSF. Chemokines selected from the group comprising IL-8, MCP-1, receptors selected from the group Tissue factor and IL-2Ralpha. and/or
- ii) decrease or inhibit the production bradykinin by the phase contact system, and/or;
- iii) decrease or inhibit the attractant potential for monocytes, and/or
- iv) decrease or inhibit the life-time of monocytes, neutrophils and other immune cells serving as an inducer of apoptosis, and/or

- v) decrease or inhibit vascular endothelial cells to express the adhesion molecules, said adhesion molecules being preferably selected from the group comprising PECAM, ICAM-1, E-selectins, VCAM-1 and/or
- 5 vi) decrease or inhibit activation of the contact phase system to produce bradykinin leading to increased vascular permeability, and/or
- vii) stimulate the synthesis of an anti-inflammatory mediator selected from the group of IL-10 and IL-12, and/or
- viii) removing endotoxin from septic patients, and/or

10 In one embodiment the anti-inflammatory peptide compound of the invention is a peptide

- i) derived from any of the sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589,
- ii) comprising one or more of the sequences set forth in SEQ ID NO: 2-587,
- 15 iii) capable of at least one of the above activities of an anti-inflammatory compound, more preferable at least two of the above activities, even more preferable at least three of the above activities, even more preferable at least four of the above activities, even more preferable at least five of the above activities, even more preferable at least six of the above activities, even more preferable at least seven of the above activities, even more preferable at least eight of the above activities, and most preferably nine of the above activities.

25 In another embodiment the invention provides an anti-inflammatory peptide capable of inhibiting the secretion of cytokine IL-6 from monocytes in response to bacterial products including, but not limited to, LPS (Lipopolysaccharide), PGN (peptidoglycan), LTA (Lipotechoic acid), MDP (muramyl dipeptide) and PCW (purified cell wall from bacteria), comprising two or more sequences set forth in SEQ ID NOS: 233-253, wherein said sequences constitute a contiguous sequence
30 derived from the sequence of pHBP set forth in SEQ ID NO: 588.

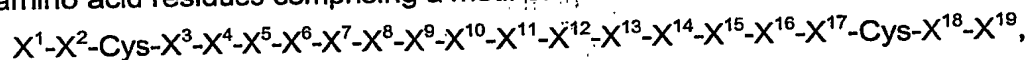
In a preferred embodiment of the invention an inflammatory peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593). Even more preferred the peptide, wherein the sequence identified in SEQ ID NO: 593 has the

N-terminal and C-terminal modified, as for example the N-terminal amino group being amidated and the C-terminal carboxy group being acetylated.

Peptides

It is an objective of the present invention to provide one or more peptides for the manufacture of a medicament for prevention and/or treatment of Gram positive and/or Gram negative infections, sepsis, severe sepsis, septic shock and/or disseminated intravascular coagulation, and/or for modulation of inflammatory response, and/or prevention of cell apoptosis.

In one embodiment the invention concerns a peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula



wherein

the side chains of the two Cys residues are connected via a disulfide bond,

wherein

X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser,

Group 2 consisting of Arg and Lys,

Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,

Group 4 consisting of Asn and Gln, or

Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

wherein

X^1 can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;

X^2 is selected from Group 5 or Group 3;

X^3 , X^{15} and X^4 are selected from Group 1;

X^5 is Thr or selected from from Group 1;

X^6 , X^{11} , X^{12} , X^{13} and X^7 are selected from Group 3;

X^8 and X^{17} are selected from Group 1, 3 or 4;

X^9 is selected from from Group 5, 1 or 3;

X^{10} is selected from from Group 2, 3 or 4;

X^{14} is Ser or selected from from Group 3;

X¹⁶ and X¹⁸ is selected from Group 1 or 3

X¹⁹ can be represented by a sequence consisting of 2-5 amino acid residues or a single amino acid residue selected from Group 5, 2, or 4, with the proviso, that when X¹ includes Pro, then X¹⁹ is Gln.

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In a preferred embodiment X¹ in sequence of the peptide of the invention is represented by an amino acid sequence selected from SEQ ID NOS: 607-612. In another preferred embodiment X¹ is Arg. Another preferred embodiment for the sequence of the peptide is Phe in position X². It is also preferred Ala or Gly as the X³ residue. The peptide preferably has Gly as the X⁴ residue. The X⁵ residue is preferably represented by Ala, and X⁶ by Leu. The X⁷ may preferably be selected from the group containing Ile, Leu, Met or Val. The peptide according to another preferred embodiment has X⁸ represented by His or Val. The position X⁹ in the sequence of the peptide may preferably be occupied by a residue selected from Ala, Phe or Pro. X¹⁰ is preferably represented by Arg, and X¹¹ is Phe or Pro. The position X¹² is preferably occupied by His or Val, and X¹³ is preferably selected from the group consisting Ile, Leu, Met or Val. The peptide has preferably Thr in position X¹⁴, Ala in position X¹⁵ and X¹⁶, and X¹⁷ is preferably Ser. The X¹⁸ residue is preferably represented by Phe. X¹⁹ in one preferred embodiment is represented by a sequence identified as SEQ ID NO: 613, and in another preferred embodiment is represented by Arg or Gln.

Another preferred embodiment of a peptide having the sequence comprising the above motif is that N-terminal and/or C-terminal of said peptide may be modified. Thus, the C-terminal carboxy group in a more preferred embodiment is amidated, and the N-terminal in another more preferred embodiment is acetylated.

Furthermore, the invention in the other preferred embodiments concerns particular amino acid sequences comprising the motif disclosed above. Thus, the peptide according to the present invention preferably has a sequence selected from KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593), NQGRHFCCGALIHARFVMTAASCFQ (SEQ ID NO: 594), KQGRHFCCGALIHARFVMTAASCFR (SEQ ID NO: 595), KQGRPFCGALIHARFVMTAASCFR (SEQ ID NO: 596), KQGRHFCCGALIHPRFVMTAASCFR (SEQ ID NO: 597),

KQGRPFCGGALIHPRFVMTAASCFR (SEQ ID NO: 598),
RFCSAATLVFRPHVLGACFPRGQK (SEQ ID NO: 599),
NQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 600),
KQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 601),
5 NQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 602),
KQGRPFCAGALVHPQFVLTAASCFR (SEQ ID NO: 603),
LRGGHFCGATLIAPNFVMSAAHCVA (SEQ ID NO: 604),
RRGGHFCGATLIARNFVMSAVHCVN (SEQ ID NO: 605) and
RSREYRCGGTLVSQRYILTAASCAA (SEQ ID NO: 606).

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The sequences identified in SEQ ID NO: 593 and 594 according to the invention are preferably modified in the N- and C-terminus as described above.

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All peptides of at most 44 amino acids length comprising the motif as above are in the scope of the present invention. However, the invention preferably concerns peptides wherein the positions X^{15} - X^{16} - X^{17} in the motif are Ala-Ala-Ser correspondingly, in positions X^1 to X^{14} and X^{18} to X^{19} may be any amino acid residues connected in a contiguous polypeptide chain. The preferred embodiments for the positions are as described above. Moreover, it is further preferred, if the peptide comprises one or more amino acid sequences are selected from SEQ ID NOS: 12-39. Another preferred embodiment if the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253. It is still another preferred embodiment if the peptide comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 34. In yet preferred embodiment the peptide comprises one or more amino acid sequences selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21. Still yet preferred embodiment is a peptide comprising one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34. Also preferred a peptide comprising one or more amino acid sequences are selected from SEQ ID NOS: 395-421.

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The sequences of the peptide may be derived from any longer polypeptide sequence of natural or artificial origin. However the invention concerns some preferred embodiments for such the sequence. In a first preferred embodiment the invention concerns one or more amino acid sequences which are derived from the

sequence of human heparin-binding protein (hHBP) set forth in SEQ ID NO: 1. In another preferred embodiment the invention concerns one or more amino acid sequences derived from the sequence of porcine heparin-binding protein (pHBP) set forth in SEQ ID NO: 588. In still another preferred embodiment the invention
5 concerns one or more amino acid sequences derived from the sequence of human neutrophil elastase set forth in SEQ ID NO: 589.

Additionally, a preferred peptide comprising the above motive according to the invention comprises one or more amino acid sequences set forth in SEQ ID NOS: 2-
10 587.

A peptide as described above according to the invention is capable of inhibiting the secretion of cytokine IL-6 from monocytes.

15 It is another objective of the present invention to produce peptides as small as possible, yet exhibiting the desired effect(s).

In one embodiment, the invention relates to providing a peptide consisting of at most 8 amino acids comprising one or more of the amino acid sequences set forth in SEQ
20 ID NOS: 2-587.

In another embodiment, the invention relates to providing a peptide consisting of at most 12 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-14, 22-36, 46-107, 115-185 and 195-587.
25

In still another embodiment, the invention relates to providing a peptide consisting of at most 16 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-14, 46-107, 115-185 and 195-587.

30 In yet another embodiment, the invention relates to providing a peptide consisting of at most 20 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-107, 115-185 and 195-587.

In yet still another embodiment, the invention relates to providing a peptide
35 consisting of at most 24 amino acids comprising one or more of the amino acid

sequences set forth in SEQ ID NOS: 46-89, 117-124, 139-157, 163-175 and 195-587.

5 In yet another embodiment, the invention relates to providing a peptide consisting of at most 28 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-52, 61-66, 73-89, 117-124, 165-175 and 195-587.

10 In still another embodiment, the invention relates to providing a peptide consisting of at most 32 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 46-52, 61-66, 73-89, 117-124, 165-175 and 195-587.

15 In still further another embodiment, the invention relates to providing a peptide consisting of at most 36 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

20 In yet another embodiment, the invention relates to providing a peptide consisting of at most 40 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

25 In yet still another embodiment, the invention relates to providing a peptide consisting of at most 44 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NO: 46-52, 61-66, 73-89, 117- 124, 165-175 and 195-587.

Furthermore, in yet another embodiment, the invention relates to providing a peptide consisting of at least 48 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 2-587.

30 According to amino acid sequences of the above peptides may be derived from the amino acid sequence of polypeptides selected from the group comprising hHBP (SEQ ID NO: 1), pHBP (SEQ ID NO: 588), or human neutrophil elastase (SEQ ID NO: 589).

In one embodiment the peptide comprises at least two of the sequences set forth above. In such embodiment it is preferred that the two or more sequences constitute a continuous sequence derived from another sequence, such as a continuous sequence derived from hHBP, or pHBP, or human neutrophil elastase.

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In another embodiment the peptide comprises at least two of the sequences set forth above. In such embodiment it is preferred that the two or more sequences are randomly selected to constitute a continuous sequence derived from another sequence, such as a random sequence derived from hHBP, or pHBP, or human neutrophil elastase.

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In the present context by the term "derived from" is meant that one amino acid sequence, such as for example a peptide amino acid sequence, is representing a fragment, or is comprising a fragment of another amino acid sequence, such as for example the amino acid sequence of a larger polypeptide: thus, the peptide amino acid sequence is derived from (originates from) the amino acid sequence of the larger polypeptide.

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In an additional embodiment the present invention relates to providing a peptide consisting of at least 24 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 233-253.

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In another additional embodiment the present invention relates to providing a peptide consisting of at least 24 amino acids and at most 224 amino acids comprising one or more of the amino acid sequences set forth in SEQ ID NOS: 286-346.

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In a preferred embodiment the present invention relates to providing a peptide having the sequence KQGRPFCAGALVHPRFVLTAASCFR set forth in SEQ ID NO: 593, or fragments of said sequence, or variants of said sequence, or fragments of said variants.

30

In another preferred embodiment the present invention relates to providing a peptide having the sequence NQGRHFCCGALIHARFVMTAASCFQ set forth in SEQ ID NO:

594, or fragments of said sequence, or variants of said sequence, or fragments of said variants.

5 By the term of "fragment" in the present context is meant that a peptide of the invention is represented by a shorter amino acid sequence which is identical to any of the amino acid sequences which the peptide comprises.

10 By the term "variant" in the present context is meant that a peptide of the invention is represented by an amino acid sequence which has at least 40% identity with the amino acid sequence of the peptide, more preferably at least 50%, even more preferably at least 60%, even more preferably at least 70%, even more preferably at least 80%, even more preferably at least 90%, even more preferably at least 95%, and most preferably at least 97%.

15 The amino acid sequence of a variant of a peptide may differ from the amino acid sequence of the peptide by an insertion or deletion of one or more amino acid residues and/or the substitution of one or more amino acid residues by different amino acid residues. Preferably, amino acid changes are of a minor nature, that is, conservative amino acid substitutions; small deletions, typically of one to about 10
20 amino acids; small amino- or carboxyl-terminal extensions; small linker sequences of about 3-15 residues; or a small extension that may facilitates purification by changing net charge or another function, such as a polyhistidine tract, an antigenic epitope or a binding domain.

25 Examples of conservative substitutions are within the group of basic amino acids (such as arginine, lysine and histidine), acidic amino acids (such as glutamic acid and aspartic acid), polar amino acids (such as glutamine and asparagine), hydrophobic amino acids (such as leucine, isoleucine and valine), aromatic amino acids (such as phenylalanine, tryptophan and tyrosine) and small amino acids (such as
30 glycine, alanine, serine, threonine and methionine). Amino acid substitutions, which do not generally alter the specific activity, are known in the art and are described, e.g., by H. Neurath and R.L. Hill, 1979, in, The Proteins, Academic Press, New York. The most commonly occurring exchanges are: Ala/Ser, Val/Ile, Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Ser/Gly, Tyr/Phe, Ala/Pro, Lys/Arg,
35 Asp/Asn, Leu/Ile, Leu/Val, Ala/Glu, Asp/Gly as well as these in reverse.

It is an additional aspect of the present invention to provide functional fragments or variants of the peptides.

- 5 By the term "functional" in relation to a peptide fragment or peptide variant in the present context is meant that the peptide fragment or peptide variant is capable to demonstrate one or more of the biological activities described below.

10 In a preferred embodiment the invention relates to providing functional fragments, variants or fragments of said variants of a peptide having the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593).

15 In another preferred embodiment the invention relates to providing functional fragments, variants or fragments of said variants of a peptide having the sequence NQGRHFCGGALIHARFVMTAASCFQ (SEQ ID NO: 594).

20 It is an object of the invention to provide a peptide, wherein said peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 having the motif cys- X_{15} -cys, wherein X_{15} represents an amino acid sequence of 15 amino acids.

25 In a further embodiment said peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 34.

In yet a further embodiment the present peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 21.

30 In another aspect the peptide comprises one or more amino acid sequences set forth in SEQ ID NOS: 233-253 and the amino acid sequence set forth in SEQ ID NO: 34 and the amino acid sequence set forth in SEQ ID NO: 21.

Furthermore, it is within the scope of the invention to provide a peptide, which

- i) comprises a sequence derived from any of the amino acid sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589, and
- ii) is capable of bactericidal activity, and/or
- iii) is an attractant for monocytes.

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In one embodiment said peptide is consisting of at most 8 amino acids, whereof at least 5 and at most 6 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

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In another embodiment the peptide is consisting of at most 12 amino acids, whereof at least 6 and at most 9 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

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In still another embodiment the peptide is consisting of most 16 amino acids, whereof at least 8 and most 12 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

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In still further another embodiment the peptide is consisting of at the most 20 amino acids, whereof at least 10 and at most 15 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

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In still yet another embodiment the peptide is consisting of at most 24 amino acids, whereof at least 12 and at most 18 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

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In yet another embodiment the peptide is consisting of at most 28 amino acids, whereof at least 14 and at most 21 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

In yet further another embodiment the peptide is consisting of at most 32 amino acids, whereof at least 16 and at most 24 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

In yet still further another embodiment the peptide is consisting of at most 36 amino acids, whereof at least 18 and at most 27 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

- 5 In a further another embodiment the peptide is consisting of at most 40 amino acids, whereof at least 20 and at most 30 amino acids are basic amino acids selected from the group comprising lysine, arginine and histidine.

Moreover, the invention also provides a peptide, which

- 10 i) comprises a sequence derived from any of the amino acid sequences set forth in SEQ ID NO: 1, SEQ ID NO: 588, or SEQ ID NO: 589, and
ii) is capable of preventing cell apoptosis.

- 15 In one embodiment said peptide is consisting of at most 8 amino acids, whereof at least 4 and at most 6 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 20 In another embodiment the peptide is consisting of at most 12 amino acids, whereof at least 6 and at most 10 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 25 In still another embodiment the peptide is consisting of at most 16 amino acids, whereof at least 8 and at most 12 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- In yet another embodiment the peptide is consisting of at most 20 amino acids, whereof at least 10 and at most 12 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

- 30 In still yet another embodiment the peptide is consisting of at most 24 amino acids, whereof at least 12 and at most 18 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

In yet further another embodiment the peptide is consisting of at most 28 amino acids, whereof at least 14 and at most 21 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

5 In yet still further another embodiment of at most 32 amino acids, whereof at least 16 and at most 24 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

10 Furthermore, in yet still further another embodiment the peptide is consisting of at most 36 amino acids, whereof at least 18 and at most 27 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

15 In a further another embodiment the peptide is consisting of at most 40 amino acids, whereof at least 20 and at most 30 amino acids are acidic amino acids selected from the group comprising aspartic acid and glutamic acid.

Screening assays

20 According to the invention recombinant or synthetically produced peptides are further screened for their biological activity.

In the present content by "biological activity of a peptide" is meant that a peptide is able to demonstrate at least one of the following biological activities: (1) heparin binding, (2) lipopolysaccharide (LPS) binding; (3) activating of protein kinase C; (4) stimulating thrombospondin secretion from monocytes; (5) stimulating/inhibiting the production of IL-1, IL-6, IL-8, GCSF, GM-CSF, M-CSF, TNF- α , MCP-1, group Tissue factor, IL-2R- α ; (6) bactericidal; (7) chemotactic for monocytes; (8) anti-apoptotic, (9) stimulating/inhibiting the vascular permeability; (10) stimulating/inhibiting the expression of adhesion molecules PECAM or ICAM1 by endothelial cells, (11) stimulating/inhibiting the production of bradykinin, (12) increase the phagocytic potential, (13) up-regulate class-II MHC.

35 In a preferred embodiment the peptide is able to demonstrate at least two of the above activities, more preferably at least three of the above activities, even more preferably at least four of the above activities (1-11), yet even more preferably at

least five of the above activities, even more preferably at least six of the above activities, even more preferably at least seven of the above activities, even more preferably at least eight of the above activities, even more preferably at least nine of the above activities, even more preferably at least ten of the above activities and most preferably the peptide is able to demonstrate at least all of the above activities.

Methods for evaluating of the above listed biological activities of peptides according to the invention are well known in art.

According to the invention there are a number of available assays for evaluating the biological activity of the present peptide.

One of such assays for the evaluation of chemotactic activity of the peptides may for example be the method of Cates et al. (in Leukocyte chemotaxis, p 67. Gallin and Quie eds, Raven Press, NY, 1978), or of Keire et al. (J. Biol. Chem. 2001, 276: 48847-53).

In another embodiment the lipopolysaccharide-binding activity of the peptides may be examined by a method described by Linde et al (Biotechniques 2000, 28:218-20).

To evaluate the bactericidal activity of the present peptides, the assay described by Shafer et al. (Infect. Immun. 1986, 53:651-55) may be used.

In one aspect measuring cell apoptosis in the presence of the present peptides may be done according to Linde et al. (Anal. Biochem. 2000, 280:186-8).

It is possible to perform an evaluation of the heparin binding capacity of the peptides by conventional chromatography on a commercially available heparin-affinity column.

The protein kinase C activation by the peptides may be done according to Pereira et al., 1996 (J. Leukoc. Biol. 60:415-22).

The changes in expression of different polypeptides, such as for example IL-1, IL-6, IL-8, TNF- α , thrombospondin, PECAM or ICAM in the presence of the peptides according to the invention may, for example, be evaluated either by reverse phase

transcriptase, immunoassay, immunoblotting, or immunostaining of the treated cells grown in culture.

5 The vascular permeability may be determined by using the assay as described by Gautam et al. in 1998 (Br J Pharmacol 1998 Nov;125(5):1109-14)

Medicament

10 It is an important objective of the present invention to use the peptides, functionally active fragments or variants of said peptides for the manufacture of a medicament for prevention and/or treatment of Gram positive and/or Gram negative infections, sepsis, severe sepsis, septic shock and/or disseminated intravascular coagulation, and/or for modulation of inflammatory response, and/or prevention of cell apoptosis.

15 In one embodiment the invention relates to the manufacture of a medicament which is capable of being used for prevention and/or treatment of Gram positive bacterial infection caused by Bacillaceae, Micrococcaceae, Mycobacteriaceae, Peptococcaceae and/or a Gram negative bacterial infection caused by Acetobacteriaceae, Alcaligenaceae, Bacteroidaceae, Chromatiaceae, Entero-
20 bacteriaceae, Legionellaceae, Neisseriaceae, Nitrobacteriaceae, Pseudomonadaceae, Rhizobiaceae, Rickettsiaceae, Spirochaetaceae, Vibrionaceae, Brucella, Chromobacterium.

25 In a preferred embodiment for prevention and/or treatment the infection by *Neisserie meningitidis* (meningococcus) and/or *Pneumococcus pneumoniae* (pneumococcus).

In another embodiment the invention relates to the manufacture of a medicament which is capable of being used for prevention and/or treatment of sepsis, severe sepsis, septic shock and disseminated intravascular coagulation.

30 It is an important objective of the invention to use the peptides for the manufacture of a medicament for stimulation of an inflammatory response, in a preferred embodiment, the inflammatory response to bacterial infection.

Another important objective of the invention is to use the peptides for the manufacture of a medicament for inhibition of an inflammatory response. Examples of inflammatory responses, which may be harmful for an individual and therefore are advantageously being suppressed include but are not limited by conditions associated with extensive trauma, or chronic inflammation, such as for example type IV delayed hypersensitivity, associated for example with infection by *Tubercle bacilli*, or systematic inflammatory response syndrome; or multiple organ failure, or rheumatoid arthritis.

In an additional embodiment of the invention to use the peptides capable of anti-apoptotic activity are used for the manufacture of a medicament for the treatment of a disease, pathological conditions whereof are associated with massive cell loss due to apoptosis. Examples of such a disease include but not limited by degenerative diseases the central and peripheral nervous system, such as postoperative nerve damage, traumatic nerve damage, e.g. resulting from spinal cord injury, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, multiinfarct dementia, multiple sclerosis, nerve degeneration associated with diabetes mellitus, neuro-muscular degeneration, schizophrenia, Alzheimer's disease, Parkinson's disease, or Huntington's disease, degenerative conditions of the gonads, of the pancreas, such as diabetes mellitus type I and II, of the kidney, such as nephrosis, or cancer.

By the term "apoptosis" in the present content is meant a programmed cell death due to activation an internal death program.

In the pharmaceutical composition of a medicament of the invention, the peptides and antibodies may be formulated by any of the established methods of formulating pharmaceutical compositions, e.g. as described in Remington's Pharmaceutical Sciences, 1985. The composition may typically be in a form suited for local or systemic injection or infusion and may, as such, be formulated with sterile water or an isotonic saline or glucose solution. The compositions may be sterilised by conventional sterilisation techniques, which are well known in the art. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilised, the lyophilised preparation being combined with the sterile aqueous solution prior to administration. The composition may contain pharmaceutically acceptable auxiliary

substances as required to approximate physiological conditions, such as buffering agents, tonicity adjusting agents and the like, for instance sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, etc. The concentration of peptides may vary widely, i.e. from less than about 0.5%, such as from 1%, to as much as 15-20% by weight. A unit dosage of the composition may typically contain from about 10 mg to about 1 g of a peptide.

The peptides and antibodies may be administered topically or by injection. Dosages will be prescribed by the physician according to the particular condition and the particular individual to be treated. Dosages and frequency is carefully adapted and adjusted according to parameters determined by the physician in charge. A preferred administration route may be e.g. subcutaneous injections. Subcutaneous, intravenous, intramuscular, intratracheal, intravesical, intratechal or intraperitoneal injections of HBP peptides and anti-HBP antibodies may be given per 24 hours in the range of from 0.1-100 mg, especially 0.1-20 mg, in particular 0.1-10 mg per kg body weight. The dose may be given 1-4 times per 24 hours or administered continuously through a catheter.

Compositions of a medicament used in the present invention comprising bioactive peptides of HBP, HBP homologous peptides or anti-HBP antibodies described below may additionally be supplemented by antibiotics, wherein said antibiotics are routinely prescribed antibiotics by the physician according to the particular condition and the particular individual to be treated. In a preferred embodiment the supplemented antibiotics are selected from but not limited by the group of beta-lactam antibiotics, comprising penicillins and cephalosporins. A medicament comprising a peptide of HBP or a fragment of a HBP homologous peptide or an anti-HBP antibody may still additionally be supplemented by a pro-inflammatory drug, or an anti-inflammatory drug, wherein said drugs are prescribed by the physician according to the particular condition and the particular individual to be treated. The supplementary pro-inflammatory drugs may for example be selected from the group comprising CSF (colony stimulating factor) drugs. The supplementary anti-inflammatory drugs may for example be selected from the group comprising antibiotics, steroids, cytostatics, or antiviral drugs.

HBP receptors and binding sites

According to the invention information concerning potential HBP receptors and binding sites is aiding the selection of the present peptides. There has been no identification of a HBP receptor, but receptor-like structures or binding sites of HBP have been identified. HBP is a dipole separated by a hydrophobic cleft and it is therefore capable to interact with both positively and negatively charge surfaces and molecules and with hydrophobic molecules and epitomes. The charged surface areas (the epitomes) of HBP are important for several of its functions. Without being bound by theory some of such functions are described below:

It has been demonstrated that HBP's positively charged epitomes bind to negatively charged macromolecules such as the heparan sulphate and chondroitin sulphate side chains of the proteoglycans (Olofsson, AM, et al. 1999), which are present at the surface of nearly every adherent mammalian cells. Proteoglycans are proteins with long carbohydrate chains of the glucosaminoglycans (GAG) type attached. They have recently been recognized as an important part of the signaling mechanism between cells. The proteoglycans are today recognized as co-receptors that can influence how e.g. the growth factor interacts with its receptor. Co-receptors affect which signal molecules bind to the receptor, how strong the interaction is or how far the signal spreads. Co-receptors regulate such decisions as when the cell divides, what type of proteins it manufactures and even if it should die. HBP has been shown to bind to the carbohydrate part (e.g. heparan sulphate) of the syndecan family of proteoglycans, which play an important role in internalization of proteins. The binding of HBP to such proteoglycans lead to uptake of HBP into endothelial cells (Olofsson, AM et al.,1999) and probably other cell types as well. Heparan sulphate and similar highly charged negative molecules of the glucosaminoglycan type may therefore serve as binding sites for HBP, mediating many of its diverse regulatory functions. In this context it is should be noted that heparan sulphate and similar glucosaminoglycans are not just simple negatively charged molecules mediating a non-specific ionic interaction. In contrast e.g. the heparan sulphate are synthesized such that very diverse and subtle variations in the structure are achieved. Accordingly, the synthesized heparan sulphate molecules may fit only very specific positively charged epitopes, such as the ones found on the surface of HBP. The heparan sulphates and similar proteoglycans with GAG side chains may therefore be seen as a proper receptor or co-receptor for HBP.

HBP may also exploit its dipolar nature by activating the contact phase system. The contact phase system consists of HMWK and three other proteins which are closely bound together on the cell surface. HMWK is a large protein consisting of 6 domains, of which one (domain 4) contains the Bradykinin sequence. An electrostatic binding from a positively charged histidin-rich area in domain 5 of HMWK to negatively charged heparan sulphate (Renne, T. et al., 2000) and chondroitin sulphate (Renne, T. et al., 2001) proteoglycans contribute significantly to the binding of HMWK to cell surfaces. The activation of the contact phase system requires that the individual components (HMWK, fXII and pre-kallikrein) are brought in close contact to each other and probably also that certain conformational changes are induced. Heparin-binding protein (HBP) has been shown to play a pivotal role in activating the contact phase system (Gautam, N. 2001), and to be capable of highly effectively displacing HMWK from GAG in an in vitro model (Renne, T. 1999). This occurs most likely by formation of two electrostatic bindings, one between the negatively charged GAG on the cell surface and HBP's strongly positively charged surface area, and another between the positively charged domain 5 of HMWK and HBP's negatively charged surface area.

Further, in addition to the above-mentioned highly charged binding sites HBP also carries other putative binding sites, such as binding sites for the Lipid A part in LPS and for interaction with and activation of Protein Kinase C (PKC), see Iversen 1997 for a review.

Monofunctional HBP peptides

The peptides according to the invention having agonistic or antagonistic properties to the putative binding sites for HBP are of considerable pharmaceutical interest as drug candidates for the prevention and/or the treatment of infections, local and systemic inflammatory disorders, asthma, systemic inflammatory response syndrome (SIRS), degenerative diseases (Alzheimer's disease), pain and other serious diseases and disorders (see table 1 in the Experimental section).

As outlined above HBP is by nature designed for initiation and regulation of local inflammatory defense to invading bacteria. In the situation of a local infection intact HBP is an ideal molecule for initiating, coordinating and regulating all the many dif-

ferent protecting mechanisms against the invading bacteria. In such situation a virulent inflammatory defense as initiated by HBP is fully appropriate and is probably needed to ensure survival of the individual. In agreement with this presumed beneficial effect of HBP, intact HBP has in animal studies been shown to be useful in prevention and treatment of severe life threatening infections and sepsis. However, in a therapeutic situation (by therapeutic is here to be understood both preventive and proper therapeutic interventions) HBP is administered differently from the natural way and therefore not all of its multiple effects may be needed or desirable.

Peptides with only one or some of the intact HBP molecule functions may therefore have significant advantages compared to the intact HBP for the treatment of specific conditions because they may be more specific, have different threshold for activation by a given process or be more powerful (displaying higher maximal efficacy).

Further, it is within the scope of the invention to provide peptides having a single function, i.e. mono-functional peptides, inhibiting specific HBP mediated processes. Below is a description of therapeutic applications, wherein the present peptides may be employed.

In the treatment of severe life threatening infections with HBP the monocyte activating and stimulating function may be the most important. To treat a lung infection for instance, HBP will most likely have to be administered systemically (e.g. as a subcutaneous injection or infusion). When administered at a site distant from the infection the ability of intact HBP to induce capillary leakage may not be advantageous, since this could lead to accumulation of neutrophils and edema formation at the administration site. While such potential side effect may be fully acceptable considering the ability of HBP to prevent or treat life-threatening infections, the use of a mono-functional HBP peptide according to the invention is to be preferred. The mono-functional peptide may have an increased ability to activate monocytes and a decreased ability to induce capillary leakage.

Monocytes play a significant role not only in eliminating bacteria but also in eliminating certain cancer cells. A mono-functional peptide with increased efficacy for stimulating the cytotoxic ability of the monocytes and macrophages would be highly desirable.

Many degenerative diseases (e.g. Alzheimer's disease) are characterized by an increased program cell death – i.e. and increased apoptosis. This means, that the cells die faster. Agents preventing or delaying apoptosis could conceivably be of use for slowing down the development of such degenerative diseases. A mono-

5 functional peptide of the invention having a high anti-apoptosis efficacy, but no inflammatory potential may be a potential candidate for intervention in degenerative diseases.

Further, while the inflammatory defense initiated and regulated by intact HBP is needed to insure elimination of local bacterial infections it is not ideally designed to combat systemic infections, which spread to the whole body. In such circumstances, the inflammatory response may lead to damages to the organs and even to death of the organism if not controlled or stopped in time. Furthermore, the organism may react with an inflammatory response in situations where there is no infection. In such

10 situations the inflammatory response is not only needless it is also highly damaging to the body. As an example, patients exposed to a trauma e.g. a car accident may develop a systemic inflammatory response caused by the extensive tissue damage. This may lead to hypotension, activation of the coagulation system, formation of clots and subsequent bleeding due to increased fibrinolysis, respiratory distress and failure of vital organs, such as the liver, kidney and the heart. The mechanisms leading to such Systemic Inflammatory Response Syndrome (SIRS) and Multiple Organ Failure (MOF) have not been fully elucidated. Without being bound by theory the interaction and contribution of HBP to the activation of the contact phase system probably plays a significant role.

According to the invention it is of significant interest to provide antagonist to HBP to use in the prevention and/or the treatment of such serious disorders. While antibodies to HBP may be highly useful in several clinical situations characterized by increased activation of the contact phase system and increased Bradykinin release,

20 small peptide HBP antagonists may have several advantages. They may be used in a wider range of diseases and disorders due to their smaller size and presumed better tissue penetration.

In another aspect of the present invention a more effective means of preventing bradykinin mediated disease processes is provided. As mentioned above anti-HBP

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antibodies are obvious candidates, but small peptide HBP antagonists of the invention may have significant advantages. Bradykinin plays a role in the development of SIRS amongst other diseases. Bradykinin exerts its effect by interaction with specific receptors. Numerous bradykinin antagonists have been synthesized in the search for new drugs, which can prevent the action of bradykinin in conditions, such as circulatory and endotoxic shock, rhinitis and other allergic conditions, chronic inflammatory diseases such as rheumatoid arthritis, and colitis ulcerosa and brain edema. Although some of them have shown to be of some clinical use the effect has in general been less than expected considering the central mediator role of bradykinin. Without being bound by theory one reason might be that an antagonist only partly blocks the effect of bradykinin, but probably more likely that the antagonist in a therapeutic situation is often given after a significant amount of bradykinin has been released and has exerted its effects on the receptors.

In a further aspects of the present invention mono-functional, non-toxic agonists which bind LPS or other endotoxins, such as PGN, LTA or other cell wall components from bacteria with the same or higher affinity as Polymyxin B would have significant therapeutic potential for the treatment of sepsis. Endotoxins from both Gram negative (LPS) and Gram positive (PGN, LTA) bacteria play a significant role in the development of septic shock. It has recently been shown that removal of endotoxin (LPS) from the blood of septic patient by passage of the patient's blood through a Polymyxin B - column significantly reduces mortality. Polymyxin B binds LPS. Polymyxin B has certain structural similarities with HBP, which also binds LPS.

Production

The peptides of the present invention may be prepared by conventional synthetic methods, recombinant DNA technologies, enzymatic cleavage of full-length proteins which the peptide sequences are derived from, or a combination of said methods.

Synthetic preparation

The methods for synthetic production of peptides are well known in art. Detailed descriptions as well as practical advice for producing synthetic peptides may be found in 'Synthetic Peptides: A User's Guide' (Advances in Molecular Biology), Grant G. A. ed., Oxford University Press, 2002, or in: 'Pharmaceutical Formulation: Development

opment of Peptides and Proteins, Frokjaer and Hovgaard eds., Taylor and Francis, 1999.

Peptides may for example be synthesised by using Fmoc chemistry and with Acm-protected cysteins. After purification by reversed phase HPLC, peptides may be further processed to obtain for example cyclic or C- or N-terminal modified isoforms. The methods for cyclization and terminal modification are well-known in the art and described in detail in the above cited manuals.

The DNA sequence encoding a peptide or full-length protein of the invention may be prepared synthetically by established standard methods, e.g. the phosphoamidite method described by Beaucage and Caruthers, 1981, Tetrahedron Lett. 22:1859-1869, or the method described by Matthes et al., 1984, EMBO J. 3:801-805. According to the phosphoamidite method, oligonucleotides are synthesized, e.g. in an automatic DNA synthesizer, purified, annealed, ligated and cloned in suitable vectors.

Recombinant preparation

The peptides of the invention may also be produced by use of recombinant DNA technologies. The DNA sequence encoding a peptide may be prepared by fragmentation of the DNA sequences encoding a full-length protein, which the peptide is derived from, using DNAase I according to a standard protocol (Sambrook et al., Molecular cloning: A Laboratory manual. 2rd ed., CSHL Press, Cold Spring Harbor, NY, 1989). The present invention relates to the full-length protein being selected from the group of proteins comprising human HBP (SEQ ID NO:1), porcine HBP (SEQ ID NO: 588) and human neutrophil elastase (SEQ ID NO: 589), said proteins being encoded by the DNA sequences set forth in SEQ ID NO: 590, SEQ ID NO: 591 and SEQ ID NO: 592, correspondingly. The DNA encoding the full-length proteins may alternatively be fragmented using specific restriction endonucleases. The fragments of DNA are further purified using standard procedures described in Sambrook et al., Molecular cloning: A Laboratory manual. 2rd ed., CSHL Press, Cold Spring Harbor, NY, 1989.

The DNA sequence encoding a full-length protein may also be of genomic or cDNA origin, for instance obtained by preparing a genomic or cDNA library and screening

for DNA sequences coding for all or part of the full-length protein by hybridization using synthetic oligonucleotide probes in accordance with standard techniques (cf. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor, 1989). The DNA sequence may also be prepared by polymerase chain reaction using specific primers, for instance as described in US 4,683,202 or Saiki et al., 1988, *Science* 239:487-491.

The DNA sequence is then inserted into a recombinant expression vector, which may be any vector, which may conveniently be subjected to recombinant DNA procedures. The choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, i.e. a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

In the vector, the DNA sequence encoding a peptide or a full-length protein should be operably connected to a suitable promoter sequence. The promoter may be any DNA sequence, which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the coding DNA sequence in mammalian cells are the SV 40 promoter (Subramani et al., 1981, *Mol. Cell Biol.* 1:854-864), the MT-1 (metallothionein gene) promoter (Palmiter et al., 1983, *Science* 222: 809-814) or the adenovirus 2 major late promoter. A suitable promoter for use in insect cells is the polyhedrin promoter (Vasudevan et al., 1992, *FEBS Lett.* 311:7-11). Suitable promoters for use in yeast host cells include promoters from yeast glycolytic genes (Hitzeman et al., 1980, *J. Biol. Chem.* 255:12073-12080; Alber and Kawasaki, 1982, *J. Mol. Appl. Gen.* 1: 419-434) or alcohol dehydrogenase genes (Young et al., 1982, in *Genetic Engineering of Microorganisms for Chemicals*, Hollaender et al., eds., Plenum Press, New York), or the TPI1 (US 4,599,311) or ADH2-4c (Russell et al., 1983, *Nature* 304:652-654) promoters. Suitable promoters for use in filamentous fungus host cells are, for instance, the ADH3 promoter (McKnight et al., 1985, *EMBO J.* 4:2093-2099) or the *tpiA* promoter.

The coding DNA sequence may also be operably connected to a suitable terminator, such as the human growth hormone terminator (Palmiter et al., op. cit.) or (for fungal hosts) the TPI1 (Alber and Kawasaki, op. cit.) or ADH3 (McKnight et al., op. cit.) promoters. The vector may further comprise elements such as polyadenylation signals (e.g. from SV 40 or the adenovirus 5' Elb region), transcriptional enhancer sequences (e.g. the SV 40 enhancer) and translational enhancer sequences (e.g. the ones encoding adenovirus VA RNAs).

The recombinant expression vector may further comprise a DNA sequence enabling the vector to replicate in the host cell in question. An example of such a sequence (when the host cell is a mammalian cell) is the SV 40 origin of replication. The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell, such as the gene coding for dihydrofolate reductase (DHFR) or one which confers resistance to a drug, e.g. neomycin, hydromycin or methotrexate.

The procedures used to ligate the DNA sequences coding the peptides or full-length proteins, the promoter and the terminator, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook et al., op.cit.).

To obtain recombinant peptides of the invention the coding DNA sequences may be usefully fused with a second peptide coding sequence and a protease cleavage site coding sequence, giving a DNA construct encoding the fusion protein, wherein the protease cleavage site coding sequence positioned between the HBP fragment and second peptide coding DNA, inserted into a recombinant expression vector, and expressed in recombinant host cells. In one embodiment, said second peptide selected from, but not limited by the group comprising glutathion-S-reductase, calf thymosin, bacterial thioredoxin or human ubiquitin natural or synthetic variants, or peptides thereof. In another embodiment, a peptide sequence comprising a protease cleavage site may be the Factor Xa, with the amino acid sequence *IEGR*, enterokinase, with the amino acid sequence *DDDDK*, thrombin, with the amino acid sequence *LVPR/GS*, or *Acharombacter lyticus*, with the amino acid sequence *XKX*, cleavage site.

Host cell

The host cell into which the expression vector is introduced may be any cell which is capable of expression of the peptides or full-length proteins, and is preferably a eukaryotic cell, such as invertebrate (insect) cells or vertebrate cells, e.g. *Xenopus laevis* oocytes or mammalian cells, in particular insect and mammalian cells. Examples of suitable mammalian cell lines are the HEK293 (ATCC CRL-1573), COS (ATCC CRL-1650), BHK (ATCC CRL-1632, ATCC CCL-10) or CHO (ATCC CCL-61) cell lines. Methods of transfecting mammalian cells and expressing DNA sequences introduced in the cells are described in e.g. Kaufman and Sharp, J. Mol. Biol. 159, 1982, pp. 601-621; Southern and Berg, 1982, J. Mol. Appl. Genet. 1:327-341; Loyter et al., 1982, Proc. Natl. Acad. Sci. USA 79: 422-426; Wigler et al., 1978, Cell 14:725; Corsaro and Pearson, 1981, in Somatic Cell Genetics 7, p. 603; Graham and van der Eb, 1973, Virol. 52:456; and Neumann et al., 1982, EMBO J. 1:841-845.

Alternatively, fungal cells (including yeast cells) may be used as host cells. Examples of suitable yeast cells include cells of *Saccharomyces* spp. or *Schizosaccharomyces* spp., in particular strains of *Saccharomyces cerevisiae*. Examples of other fungal cells are cells of filamentous fungi, e.g. *Aspergillus* spp. or *Neurospora* spp., in particular strains of *Aspergillus oryzae* or *Aspergillus niger*. The use of *Aspergillus* spp. for the expression of proteins is described in, e.g., EP 238 023.

Culture medium

The medium used to culture the cells may be any conventional medium suitable for growing mammalian cells, such as a serum-containing or serum-free medium containing appropriate supplements, or a suitable medium for growing insect, yeast or fungal cells. Suitable media are available from commercial suppliers or may be prepared according to published recipes (e.g. in catalogues of the American Type Culture Collection).

The peptides or full-length proteins recombinantly produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, e.g. ammonium sulphate, purification by a variety of chromatographic procedures, e.g. HPLC, ion exchange chromatography, affinity chromatography, or the like.

Experimentals

Identification of and screening for active HBP peptide sequences

5 Any HBP peptide sequence with 4 or more amino acid residues may be able to exercise an agonistic or antagonistic function against one or more of HBP putative binding sites or receptors (for simplicity just called HBP receptors below). However, certain sequences and surface areas may be identified as more interesting than others. Several measures to identify potentially interesting sequences with agonistic
10 or antagonistic functions to HBP receptors were taken.

Firstly, the peptide sequence of HBP and proteins closely similar to HBP within the same species i.e. Homo sapiens were investigated. HBP is structurally very similar to human neutrophil elastase (hHNE), and specific HBP functions may be found in
15 the areas of human HBP, which are non identical to the sequences of hHNE, i.e. in the areas of the HBP molecule, which have not been conserved during evolution.

Secondly, it is hypothesized that such peptide sequences in HBP, which are conserved between species might be of particular interest.

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Thirdly, it is hypothesized that sequences in other species than Homo sapiens e.g. the pig which are closely similar but not identical to the corresponding human sequence might have other abilities than the human sequence, e.g. be antagonistic instead of agonistic.

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Finally, it is hypothesized that among the sequences identified as outlined above, the more interesting sequences may have to be found on the surface of the molecule. As the two more important known receptor-like surface areas (epitopes) are both highly charged it is hypothesized that sequences with high density of charged
30 amino acids would be of particular interest.

Screening of HBP peptide sequences for biological activity

Among the many sequences identified by the above approach, only some will have desirable biological and pharmaceutical functions. The number of possible combinations (i.e. different amino acid sequences) is astronomical. As an example the theo-
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retical number of different peptides consisting of 25 amino acids is 3.36×10^{32} . Even though some sequences based on the above outlined considerations can be identified as more interesting than others, a high number of different peptides will have to be screened for interesting biological and pharmaceutical properties.

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It is therefore important to have highly reliable high capacity assay systems to identify HBP peptides and analogues hereof with pharmaceutical potential. In this context it should be realized that testing of peptides to be useful for preventive or therapeutic purposes in humans, should be done in a human system. Intact HBP from one species does not necessarily react identical in other species and use of an animal test system e.g. a rat system for screening of the biological functions of an HBP derived peptide to be used in humans could easily be misleading. Below examples on screening assays to be used for identification of peptides with pharmaceutical potential for prevention and treatment of infectious diseases (e.g. pneumonia), severe inflammatory disorders (e.g. SIRS) and degenerative disorders (e.g. Alzheimer's disease) are presented.

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Example 1: Screening for inflammatory and anti-inflammatory potential of HBP derived peptide.

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Human whole blood (WB) contains besides red cells, platelets and plasma the white blood cells including the neutrophils and monocytes. Neutrophils and monocytes have receptors for bacterial products such as LPS, PGN and LTA. The bacterial products react directly or via specific binding proteins to receptors on the monocytes thereby stimulating them to secrete and release inflammatory cytokines comprising, but not limited to IL-1, IL-6, and TNF- α . HBP has in itself no measurable effect on cytokine secretion, but significantly amplifies cytokine synthesis and secretion induced by bacterial products. In the assay type described the amplification of 160 μ mol HBP per ml WB in general leads to at least three-fold amplification of the cytokine secretion.

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In the example to be described LPS from the E. coli is used to stimulate the monocytes in WB (anti-coagulated by use of citrate) and the activity is measured by subsequently quantifying IL-6 in plasma separated from WB. The activity of HBP, HBP derived peptides and analogues hereof are evaluated by their ability to:

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1. increase IL-6 secretion in absence of bacterial products
2. increase IL-6 secretion in presence of bacterial products
3. decrease IL-6 secretion in presence of bacterial products
- 5 4. inhibit amplification of cytokine secretion induced by intact HBP

10 An ideal HBP peptide agonist will display the same ability as intact HBP itself in this system, i.e. it will have no activity itself when added to WB but when added simultaneously with LPS or another bacterial product it should stimulate the IL-6 secretion with a factor of at least 3, preferably 4 or more. If the peptide itself stimulates IL-6 secretion in options or of LPS or other bacterial products, it may lead to a systemic hyper-inflammation in organism which is not desirable.

Reagents and methods

- 15 All operations must be carried out in LAF cabinet by observance of stringent aseptic techniques. All test tubes, pipette tips etc. must be pyrogen-free. Buffers must be prepared by use of sterile, pyrogen water, preferably water for injection. Use 0.1 % pyrogen-free BSA/PBS for all dilutions.
- 20 Add 20 μ l of HBP derived peptide (in concentrations from 25 to 2500 μ M) to 100 μ l freshly drawn (less than 4 hours old) citrate whole blood from a healthy human volunteer. Add 20 μ l bacterial component (LPS, LTA or PGN) in concentrations from 5 to 5000 ng/ml, preferably 50 to 500 ng/ml. Mix well and incubate for 16-18 hours in an atmosphere of 5 % carbon dioxide and at least 95 % relative humidity. At the end
- 25 of the incubation add at least 5 volumes (700 μ l) 0.1 % BSA/PBS. Mix well. Centrifuge 10 min. at 10.000 g. Aspirate 500 μ l supernatant. Determine the level of IL-6 by a specific human immune assay for human IL-6 with sensitivity of at least 3 pg/ml, e.g. Human IL-6 Kit from RnD Systems (cat. no. D 6050).
- 30 Negative controls: 100 μ l WB plus 40 μ l 0.1 % BSA/PBS. Positive control: 100 μ l WB plus 20 μ l LPS (same concentration as used for testing the peptide) and 20 μ l 0.1 % BSA/PBS.

Example 2: Screening for anti-apoptotic potential of HBP derived peptides and analogues

5 The screening for anti-apoptotic peptides is carried out essentially as described by Shrotri MS. et al., 2000.

Isolation of human neutrophils (PMNs)

10 Peripheral blood from normal volunteers was collected and PMNs were separated by density gradient using Ficoll-Hypaque (Sigma Chemical Co.). PMNs obtained were divided into 1-ml samples with 3.0×10^6 cells/ml and were treated and analyzed as per the protocols described below.

Cell Fixation and Staining Protocol for Analysis of Apoptosis

15 Cell pellets were obtained by centrifugation at 300g and fixed with 1% paraformaldehyde for 15 min at 4°C. Cells were washed twice and permeabilized with 70% ice-cold ethanol and stored at -20°C. Cells samples were washed twice and stained by the terminal dUTP nick-end labeling (TUNEL) assay using the APO-BRDU kit (Phoenix Flow Systems, San Diego, CA), following the manufacturer's instructions.

20 Briefly, in this assay, the enzyme terminal deoxynucleotidyl transferase (TdT) catalyzes the addition of nucleotides to DNA strand breaks in the apoptotic cells, which are subsequently labeled with fluorescein isothiocyanate (FITC)-conjugated antinucleotide antibodies. The fluorescent cells are the apoptotic cells that are then identified or assessed using the flow cytometer (EPICS Elite, Beckman-Coulter, Hialeah,

25 FL). These apoptotic cells were also visually confirmed by confocal microscopy (Meridian Instruments Inc., Okemos, MI).

Time zero group. Certain samples were fixed immediately after isolation, permeabilized, and stored at -20°C for TUNEL assay, as described earlier. These samples

30 were designated as time zero, in which no culturing was involved.

24-h culture groups. Certain samples were re-suspended after isolation in 10% fetal bovine serum (serum-enriched group) with 25 µg of control protein (BSA) or 25 µg of HBP per ml. sample. Samples were incubated in 0% serum or RPMI (serum-deprived group) with control protein, HBP or HBP derived peptide. After 24 h culture

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in a humidified CO₂ incubator, cells were fixed, permeabilized, and stored at 220°C for later TUNEL assay, as described above.

Identification of anti-apoptotic peptides

- 5 Addition of 25 µg HBP per ml sample typically decreases apoptosis from about 70 % to 45 %. Peptides decreasing apoptosis to the same or greater extent when used in equimolar amounts should be considered anti-apoptotic.

Example 3: Identification of a highly potent anti-inflammatory HBP peptide

- 10 As an example on the use of the methods outlined above to predict an HBP peptide sequence it is disclosed how a highly anti-inflammatory novel HBP peptide sequence is identified.

- 15 The innate immune response is activated by pattern recognition receptors (toll like receptors) on monocytes, neutrophils and other immune cells. HBP increase the sensitivity of these pattern recognition receptors for their response to the specific pattern motifs on the cell wall of both gram negative and gram positive bacteria as well as on fungi and other infective agents. Serine proteases and more important serine proteases with mutations in the catalytic site, but with a highly conserved serine protease fold such as HBP, play a pivotal role in innate immunity. Invertebrates have only innate immune response as the specific immune system was first developed with the evolution of the bonefish. Several serine proteases with mutations in the active site has been studied in a number of invertebrates and the *Trichoplusia ni* larval has an HBP-like serine protease. The hallmark in the mutation in the active site in the HBP from man, pig and *Trichoplusia ni* is an Histidin (H) to Serine (S) mutation, a conserved Aspartic acid (D) whereas the Serine (S) mutation is random. The active site with these mutations is therefore highly likely involved in the mechanism of action of the HBP family.

30 Method

In the present context the term "h20-44" covers the human heparin binding protein sequence of amino acids numbers 20-44. Further, by the term "p20-44" is meant the porcine heparin binding protein sequence of amino acids numbers 20-44.

The human (h20-44) and porcine (p20-44) peptides were synthesized and tested in the screening assay described in Example 1. The following parameters were examined: (a) ability to induce inflammation on their own (i.e. in the absence of any bacterial component), (b) ability to amplify or inhibit inflammation induced by a bacterial component, such as LPS from the Gram negative bacteria *E. coli* and PGN or Purified Cell Wall (PCW) from a Gram positive bacteria. As measure for immune stimulation secretion of the release of IL-6 in citrated whole blood was used. The peptides were tested in the concentrations 0.09, 0.18, 0.36 and 0.71 mg/ml blood. LPS was used at the concentration 100 ng/ml blood and PGN and PCW were used at 50 μ g/ml blood.

Results

Human HBP 20-44 peptide induced a significant and dose-dependent increase in IL-6 secretion, whereas porcine HBP 20-44 displayed no significant or dose-dependent effect (see Figure 1).

In blood stimulated with 100 ng/ml LPS, human HBP 20-44 did not significantly increase the IL-6 secretion up to 0.36 mg/ml peptide. At 0.71 mg/ml, human HBP 20-44 increased IL-6 secretion significantly, but the effect of human HBP 20-44 and LPS together was slightly less (12,130 pg/ml) than the sum of the IL-6 secretion induced by LPS and human HBP 20-44 individually (14,178 pg/ml) (see Figure 2). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the LPS induced IL-6 secretion.

In blood stimulated with PGN (50 μ g/ml) from *Staphylococcus aureus* human HBP 20-44 increased IL-6 secretion in dose-dependent way (see Figure 3). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the PGN induced IL-6 secretion.

In blood stimulated with PCW (50 μ g/ml) from *Staphylococcus aureus* human HBP 20-44 increased IL-6 secretion in dose-dependent way (Figure 4). In contrast porcine HBP 20-44 peptide significantly and dose-dependently inhibited the PCW induced IL-6 secretion.

Conclusion

Human HBP 20-44 peptide surprisingly by itself significant stimulate secretion of the pro-inflammatory cytokine IL-6. In the presence of bacterial components human HBP 20-44 to some extent further increases the immune stimulation induced by the bacterial products. Human HBP 20-44 has previously been thought to act via its ability to bind to LPS and was presumed to be an LPS neutralizing agent. An LPS neutralizing agent would inhibit the immune response, but here it is shown that human HBP 20-44 is instead a powerful immune stimulating agent. In contrast the structurally very similar porcine HBP 20-44 peptide, which only deviates from its human counterpart by 7 amino acid substitutions was found to be a highly potent anti-inflammatory agent, which significantly decreases inflammation induced by bacterial components from both Gram negative and Gram positive bacteria. Porcine HBP 20-44 peptide thus holds significant potential for becoming a broadly applicable anti-inflammatory agents with indications ranging form treatment of chronic inflammatory diseases over re-perfusion injuries in myocardial and brain insults to the life-threatening systemic inflammatory response syndrome.

Example 4: Modification of the C-terminal and N-terminal amino acid residues in hHBP and pHBP.

In human blood stimulated with 250 ug/ml PGN from *S. aureus*, hHBP 20-44 acetylated at the N-terminal amino group and amidated at the C-terminal carboxyl group stimulated the IL-6 secretion in a dose dependant way (figure 5). In figure 5 the IL-6 response has been normalized to the effect of PGN alone. Compared to figure 2 it appears that there is a more than ten fold stimulation of the PGN mediated IL-6 production for the N- and C-terminal substituted peptide.

Example 5: Essential amino acid residues in hHBP and pHBP involved in regulation of IL-6 production.

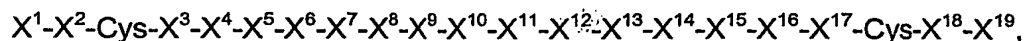
From figures 7 and 8 it can be seen that when pHBP 20-44 was acetylated and amidated at the N- and C-terminal amino acids, respectively, the variant peptide became more inhibitory to the LPS and PGN induced IL-6 production compared to the unsubstituted peptide.

In order to identify essential amino acid residues in human and porcine HBP 20-44 involved in the effects observed (see figures 1 – 4), several variants with amino acid substitutions in defined positions were tested. From figure 6 it appears that the substitution of arginine to glutamine in position 34 of pHBP 20-44 completely abolished the inhibitory effect of the peptide in the presence of PGN.

From figures 7 and 8 it appears that when the N-terminal amino acid residue of the pHBP 20-44 was substituted with the human N-terminal amino acid residue, the variant became less inhibitory compared to the original porcine peptide in the presence of both LPS and PGN. When both the N- and C-terminal amino acid residues of hHBP 20-44 was substituted with the corresponding porcine amino acid residues, the variant became nearly non-stimulating compared to the unsubstituted human peptide in the presence of LPS and in the presence of PGN the substituted peptide became inhibitory to the IL-6 production. From figures 7 and 8 it also appears that the same pattern was observed when the C-terminal amino acid residue in hHBP 20-44 was replaced with the porcine C-terminal amino acid residue, or when C-terminal amino acid residue in pHBP 20-44 was replaced with the human C-terminal amino acid residue.

Claims

1. A peptide having a sequence of at most 44 amino acid residues comprising a motif of the formula



wherein

- X can be an amino acid sequence or a single amino acid residue selected either from Group 1 consisting of Ala, Gly, and Ser;
 Group 2 consisting of Arg and Lys,
 Group 3 consisting of His, Ile, Leu, Met, Phe, Pro, Thr, Val, Trp, and Tyr,
 Group 4 consisting of Asn and Gln, or
 Group 5 consisting of Ala, Asn, Arg, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val,

wherein

- X^1 can be represented by a sequence consisting of 2-5 amino acid residues or an amino acid residue selected from Group 2;
 X^2 is selected from Group 5 or Group 3;
 X^3 , X^{15} and X^4 are selected from Group 1;
 X^5 is Thr or selected from Group 1;
 X^6 , X^{11} , X^{12} , X^{13} and X^7 are selected from Group 3;
 X^8 and X^{17} are selected from Group 1, 3 or 4;
 X^9 is selected from Group 5, 1 or 3;
 X^{10} is selected from Group 2, 3 or 4;
 X^{14} is Ser or selected from Group 3;
 X^{16} and X^{18} is selected from Group 1 or 3;
 X^{19} can be represented by a sequence consisting of 2-5 amino acid residues or a single amino acid residue selected from Group 5, 2, or 4,

with the proviso, that when X^1 includes Pro, then X^{19} is Gln.

2. The peptide according to claim 1, wherein X¹ is represented by an amino acid sequence selected from SEQ ID NOS: 607-612.
3. The peptide according to claim 1 or 2, wherein X¹ is Arg.
- 5 4. The peptide according to any of the claims 1-5, wherein X² is Phe.
5. The peptide according to any of the claims 1-6, wherein X³ is Ala or Gly.
6. The peptide according to any of the claims 1-7, wherein X⁴ is Gly.
- 10 7. The peptide according to any of the claims 1-8, wherein X⁵ is Ala.
8. The peptide according to any of the claims 1-9, wherein X⁶ is Leu.
- 15 9. The peptide according to any of the claims 1-10, wherein X⁷ is Ile, Leu, Met or Val.
10. The peptide according to any of the claims 1-11, wherein X⁸ is His or Val.
- 20 11. The peptide according to any of the claims 1-12, wherein X⁹ is Ala, Phe or Pro.
12. The peptide according to any of the claims 1-13, wherein X¹⁰ is Arg.
13. The peptide according to any of the claims 1-14, wherein X¹¹ is Phe or Pro.
- 25 14. The peptide according to any of the claims 1-15, wherein X¹² is His or Val.
15. The peptide according to any of the claims 1-16, wherein X¹³ is Ile, Leu, Met or Val.
- 30 16. The peptide according to any of the claims 1-17, wherein X¹⁴ is Thr.
17. The peptide according to any of the claims 1-18, wherein X¹⁵ is Ala.
- 35 18. The peptide according to any of the claims 1-19, wherein X¹⁶ is Ala.

19. The peptide according to any of the claims 1-20, wherein X¹⁷ is Ser.
20. The peptide according to any of the claims 1-21, wherein X¹⁸ is Phe.
- 5 21. The peptide according to any of the claims 1-22, wherein X¹⁹ is a sequence identified as SEQ ID NO: 613
- 10 22. The peptide according to claims any of the claims 1-23, wherein X¹⁹ is Arg or Gln.
23. The peptide according to claim 3, wherein the N-terminal of the polypeptide chain is modified.
- 15 24. The peptide according to claim 4, wherein the N-terminal amino group is acetylated.
25. The peptide according to claim 24, wherein the C-terminal of the polypeptide chain is modified.
- 20 26. The peptide according to claim 25, wherein the C-terminal carboxy group is amidated.
27. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRHFCCGALIHARFVMTAASCFR (SEQ ID NO: 595).
- 25 28. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCCGALIHARFVMTAASCFR (SEQ ID NO: 596).
- 30 29. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRHFCCGALIHPRFVMTAASCFR (SEQ ID NO: 597).
- 35 30. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCCGALIHPRFVMTAASCFR (SEQ ID NO: 598).

31. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RFCSAATLVFRPHVLGACFPRGQK (SEQ ID NO: 599).
- 5 32. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 600).
33. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 601).
- 10 34. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRPFCAGALVHPRFVLTAASCFQ (SEQ ID NO: 602).
35. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPQFVLTAASCFR (SEQ ID NO: 603).
- 15 36. The peptide according to any of the claims 1-26, wherein said peptide has the sequence LRGGHFCGATLIAPNFVMSAAHCVA (SEQ ID NO: 604).
37. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RRGHFCGATLIARNFVMSAVHCVN (SEQ ID NO: 605).
- 20 38. The peptide according to any of the claims 1-26, wherein said peptide has the sequence RSREYRCGGTLVSQRYILTAASCAA (SEQ ID NO: 606).
- 25 39. The peptide according to any of the claims 1-26, wherein said peptide has the sequence NQGRHFCGGALIHARFVMTAASCFQ (SEQ ID NO: 594).
40. The peptide according to any of the claims 1-26, wherein said peptide has the sequence KQGRPFCAGALVHPRFVLTAASCFR (SEQ ID NO: 593).
- 30 41. The peptide according to claim 39 or 40, wherein the C-terminal carboxy group of said peptide is amidated and/or the N-terminal amino group is acetylated.

42. The peptide according to claim 1, wherein the motif comprises a sequence of the formula Cys-X₍₁₁₎-Ala-Ala-Ser-Cys, wherein X₍₁₁₎-represents a contiguous sequence of 11 amino acids.
- 5 43. The peptide according to claims 1, 2, or 42, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 12-39.
44. The peptide according to claims 1-26 or 42 wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253.
- 10 45. The peptide according to claims 1-26 or 42 and 44, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 34.
- 15 46. The peptide according to claims 1-26 or 42 and 44-45, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21.
- 20 47. The peptide according to claims 1-26 or 42 and 44-45, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34.
48. The peptide according to claims 1-26 and 42, wherein the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 395-421.
- 25 49. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of human heparin-binding protein (hHBP) set forth in SEQ ID NO: 1.
- 30 50. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of porcine heparin-binding protein (pHBP) set forth in SEQ ID NO: 588.

51. The peptide according to claims 1-26 and 42, wherein the one or more amino acid sequences are derived from the sequence of human neutrophil elastase set forth in SEQ ID NO: 589.
- 5 52. The peptide according to claims 1-26 and 42 comprising one or more amino acid sequences set forth in SEQ ID NOS: 2-587.
53. The peptide according to any of the claims 1-52, wherein said peptide is capable of inhibiting the secretion of cytokine IL-6 from monocytes.
- 10 54. The peptide according to any of the claims 1-52, wherein said peptide is capable of stimulating the secretion of cytokine IL-6 from monocytes.
55. A process for the production of a peptide as defined in any of the claims 1-54, comprising the steps of
- 15 a) providing an expression vector containing a DNA sequence encoding one or more of the amino acid sequences as defined in the claims 1-54,
- 20 b) transforming host cells with the vector of step (a);
- c) culturing the transformed cells of step (b);
- d) purifying the expressed peptide.
- 25 56. The process according to claim 55, wherein the host cells are selected from the group comprising recombinant bacterial, yeast, insect or mammalian cells.
57. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of Gram negative bacterial infection.
- 30 58. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of Gram positive bacterial infection.
- 35

59. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of sepsis, severe sepsis, septic shock and disseminated intravascular coagulation.
- 5 60. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of meningitis.
61. The use according to claim 58, wherein meningitis is meningococcal meningitis.
- 10 62. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the treatment of pneumonia.
63. The use according to claim 60, wherein pneumonia is pneumococcal pneumonia.
- 15 64. Use of one or more peptides as defined in any of the claims 1-52 and 54 for the manufacture of a medicament for the stimulation of inflammatory response.
65. Use of one or more peptides as defined in any of the claims 1-53 for the manufacture of a medicament for the inhibition of inflammatory response.
- 20 66. Use of one or more peptides as defined in any of the claims 1-54 for the manufacture of a medicament for the prevention of cell apoptosis.
- 25 67. Use of a peptide comprising two or more sequences set forth in SEQ ID NOS: 20-36, wherein said sequences constitute a contiguous sequence derived from the sequence of human HBP set forth in SEQ ID NO:1 for the manufacture of a medicament for the treatment of individuals having suppressed immune system, cancer, auto-immune diseases and/or trauma.
- 30 68. The use according to claim 67, wherein the peptide is having the sequence identified in SEQ ID NO: 594, fragments, or variants thereof.

69. The use according to claim 68, wherein the peptide has the N-terminal amino group acetylated and/or C-terminal carboxy group amidated.

5 70. Use of a peptide comprising the sequence comprises one or more amino acid sequences are selected from SEQ ID NOS: 233-253 and SEQ ID NO: 21 and SEQ ID NO: 34, wherein said sequences constitute a contiguous sequence derived from the sequence of porcine HBP set forth in SEQ ID NO: 588 for the manufacture of a medicament for the treatment of individuals to suppress a sustained inflammatory response.

10

71. The use according to claim 70, wherein the peptide is having the sequence identified in SEQ ID NO: 593, fragments, or variants thereof.

15 72. The use according to claim 71, wherein the peptide has the N-terminal amino group acetylated and/or C-terminal carboxy group amidated.

73. A pharmaceutical composition comprising a peptide as defined in claims 1-54.

Table 1

HBP function	Mono-functional agonist	Mono-functional antagonist
Capillary leakage		Edema, SIRS
Chemotaxis	Wound healing, local infections	Re-perfusion injury, brain edema
Monocyte activation	Local and systemic infections, (tumors)	Inflammatory diseases, SIRS
Activation contact phase system	(Infection)	SIRS, post-operative bleeding, pain, (inflammation)
Anti-apoptosis	Degenerative diseases	(Tumors)
Endotoxin binding	Endotoxin removal from septic patients	

Potential applications for mono-functional peptides

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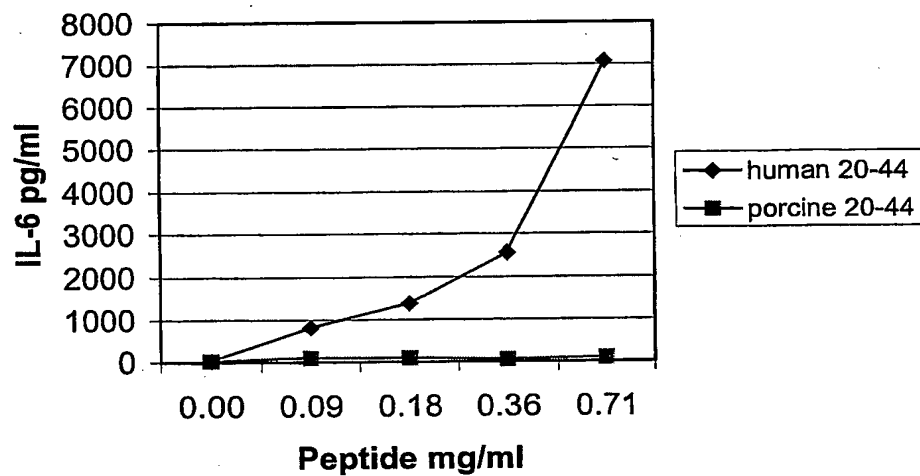
**Effect of 20-44 peptides in absence of
endotoxin**

Figure 1

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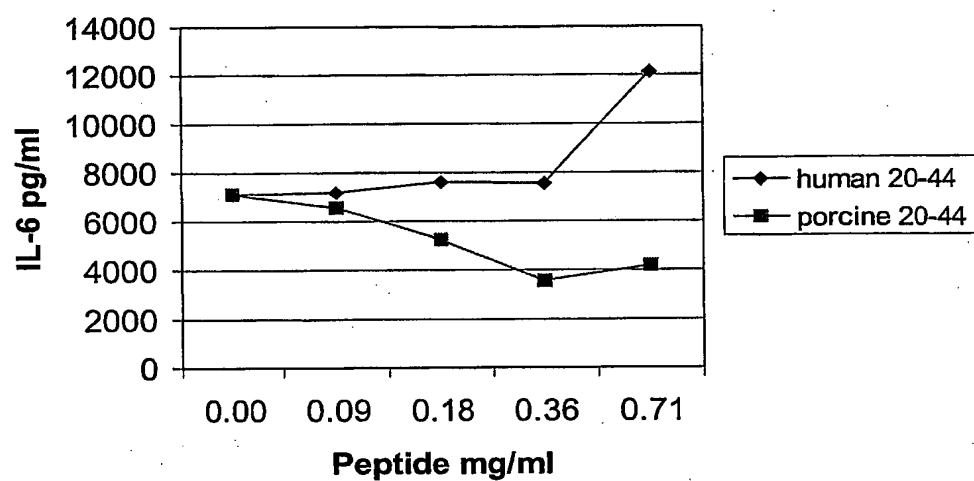
Effect of 20-44 peptides in presence of LPS

Figure 2

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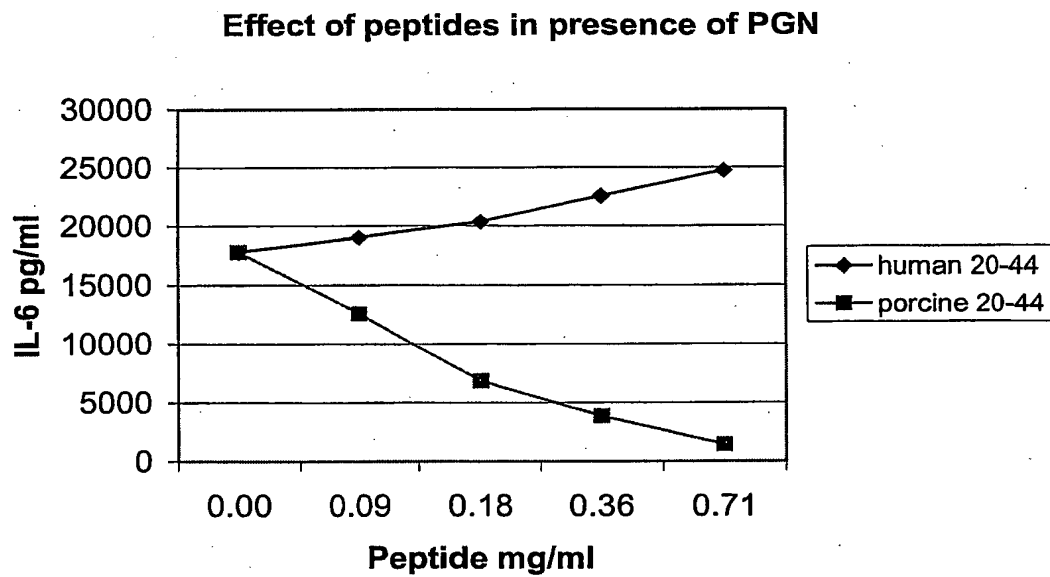


Figure 3

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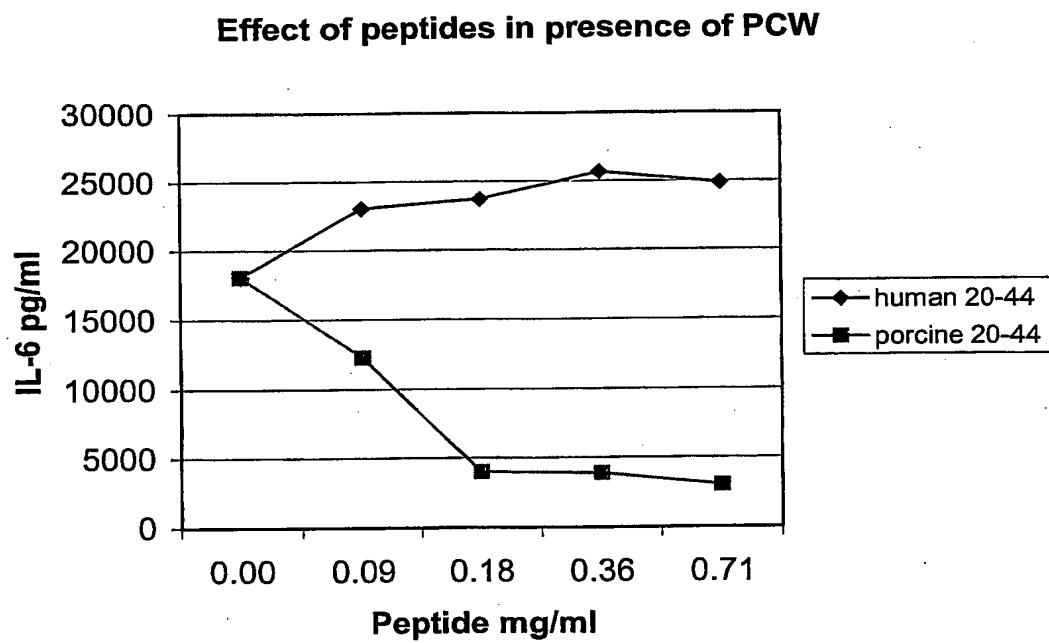


Figure 4

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**Effect of HBP 20-44 peptides
on LPS induced IL-6 secretion in the presence of PCW**

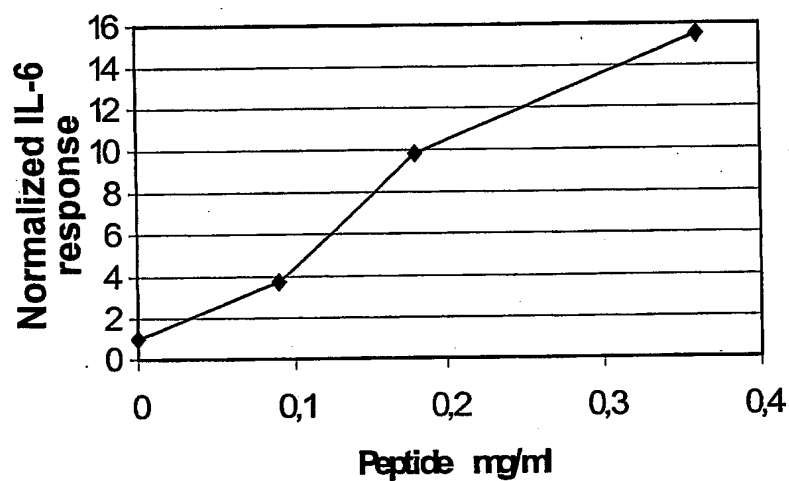


Figure 5

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Effect of N-Ac, C-amido hHBP 20-44 on PGN induced IL-6 secretion

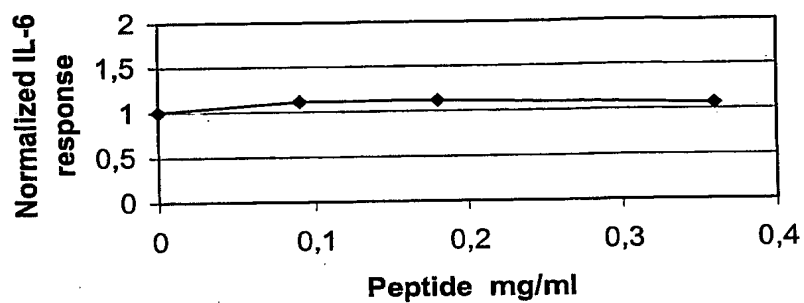


Figure 6

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**Effect of different substitutions in the sequence of hHBP and p HBP
on production of IL-6 induced by LPS.**

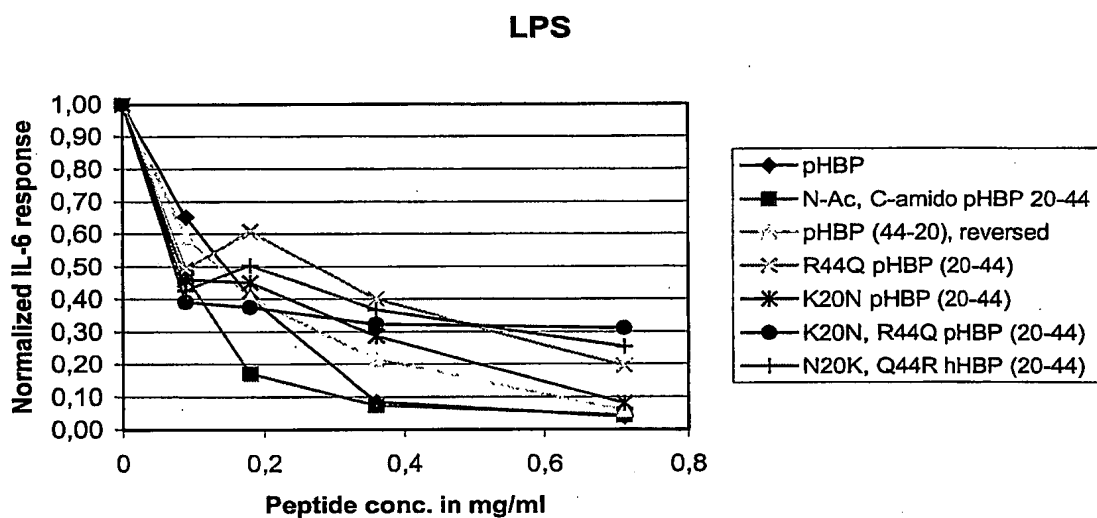


Figure 7

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**Effect of different substitutions in the sequence of hHBP and p HBP
on production of IL-6 induced by PGN**

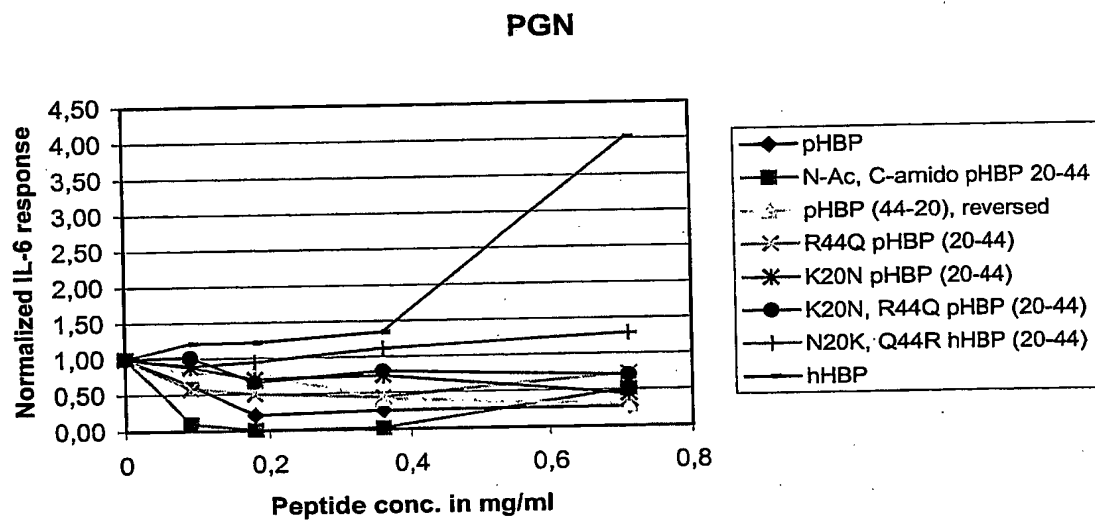


Figure 8

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Gly Val Ser Thr Val Val Leu Gly Ala Tyr Asp Leu Arg Arg Arg Glu
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Arg Gln Ser Arg Gln Thr Phe Ser Ile Ser Ser Met Ser Glu Asn Gly
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Tyr Asp Pro Gln Gln Asn Leu Asn Asp Leu Met Leu Leu Gln Leu Asp
 85 90 95

Arg Glu Ala Asn Leu Thr Ser Ser Val Thr Ile Leu Pro Leu Pro Leu
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Gln Asn Ala Thr Val Glu Ala Gly Thr Arg Cys Gln Val Ala Gly Trp
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Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val
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Asn Val Thr Val Thr Pro Glu Asp Gln Cys Arg Pro Asn Asn Val Cys
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Thr Gly Val Leu Thr Arg Arg Gly Gly Ile Cys Asn Gly Asp Gly Gly
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Thr Pro Leu Val Cys Glu Gly Leu Ala His Gly Val Ala Ser Phe Ser
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Arg Glu Ala Asn
1

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Glu Ala Asn Leu

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Ala Asn Leu Thr

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<211> 4

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<223> Peptide fragment: amino acid residues 101-104 of hHBP

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Asn Leu Thr Ser

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Leu Thr Ser Ser

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Thr Ser Ser Val

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Ser Ser Val Thr

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Ser Val Thr Ile

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Val Thr Ile Leu

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Thr Ile Leu Pro

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Ile Leu Pro Leu

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Leu Pro Leu Pro

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Pro Leu Pro Leu

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Leu Pro Leu Gln

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Pro Leu Gln Asn
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Thr Arg Cys Gln

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Cys Gln Val Ala

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Gln Val Ala Gly

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Val Ala Gly Trp

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Trp Gly Ser Gln

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Gly Ser Gln Arg

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Gln Arg Ser Gly

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Arg Phe Pro Arg
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Arg Phe Val Asn
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Phe Val Asn Val
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Arg Pro Asn Asn
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Pro Asn Asn Val
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Asn Asn Val Cys

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Asn Val Cys Thr

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Val Cys Thr Gly

1

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Cys Thr Gly Val

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Thr Gly Val Leu

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Gly Val Leu Thr

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<210> 158

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Val Leu Thr Arg

1

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Leu Thr Arg Arg

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<210> 160

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Arg Arg Gly Gly
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Arg Gly Gly Ile
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Gly Gly Ile Cys
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Gly Ile Cys Asn
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Ile Cys Asn Gly
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Cys Asn Gly Asp
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Gly Gly Thr Pro
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Thr Pro Leu Val
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<210> 173
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Pro Leu Val Cys

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<210> 174

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<400> 174

Leu Val Cys Glu

1

<210> 175

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Val Cys Glu Gly

1

<210> 176

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Cys Glu Gly Leu

1

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Glu Gly Leu Ala

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Gly Leu Ala His

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<210> 179

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Leu Ala His Gly

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Ala His Gly Val

1

<210> 181

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His Gly Val Ala

1

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Gly Val Ala Ser

1

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<400> 183

Val Ala Ser Phe

1

<210> 184

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<400> 184

Ala Ser Phe Ser

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<210> 185

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Ser Phe Ser Leu

1

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Phe Ser Leu Gly
1

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Ser Leu Gly Pro
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Leu Gly Pro Cys
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Gly Pro Cys Gly
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Cys Gly Arg Gly
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Gly Arg Gly Pro
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Arg Gly Pro Asp
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Gly Pro Asp Phe

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Pro Asp Phe Phe

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Asp Phe Phe Thr

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Phe Phe Thr Arg

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Phe Thr Arg Val
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Arg Val Ala Leu
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Val Ala Leu Phe
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Ala Leu Phe Arg

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Leu Phe Arg Asp
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<400> 204

Phe Arg Asp Trp
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<210> 205
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Arg Asp Trp Ile
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<210> 206
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Asp Trp Ile Asp
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Trp Ile Asp Gly
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Ile Asp Gly Val
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Asp Gly Val Leu
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Gly Val Leu Asn
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Val Leu Asn Asn
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Ileu Asn Asn Pro
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Asn Asn Pro Gly
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Asn Pro Gly Pro
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Pro Gly Pro Gly

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Gly Pro Gly Pro

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<211> 4

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Pro Gly Pro Ala

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Gly Gly Arg Lys

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Gly Arg Lys Ala
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Arg Lys Ala Arg
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Lys Ala Arg Pro
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Gly Gly Arg Arg
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Gly Arg Arg Ala

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Ala Gln Pro Gln
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Gln Pro Gln Glu
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Pro Gln Glu Phe
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Gln Glu Phe Pro
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Glu Phe Pro Phe
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Phe Pro Phe Leu
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Pro Phe Leu Ala

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Gln Gly Arg Pro

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Gly Arg Pro Phe

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Arg Pro Phe Cys

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Pro Phe Cys Ala

1

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Phe Cys Ala Gly

1

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Cys Ala Gly Ala

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<400> 239

Ala Gly Ala Leu

1

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Gly Ala Leu Val
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Ala Leu Val His
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Leu Val His Pro
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Val His Pro Arg
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His Pro Arg Phe
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Ser Ile Gln Lys
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Arg Phe Val Leu
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Phe Val Leu Thr
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Val Leu Thr Ala
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Leu Thr Ala Ala
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Ser Cys Phe Arg
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Cys Phe Arg Gly
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Phe Arg Gly Lys
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Arg Gly Lys Asn

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Gly Lys Asn Ser

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Lys Asn Ser Gly

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Asn Ser Gly Ser

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Ser Gly Ser Ala

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Gly Ser Ala Ser

1

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Ser Ala Ser Val

1

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Ala Ser Val Val

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Ser Val Val Leu

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Asp Leu Arg Gln

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<400> 263

Leu Arg Gln Gln

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<400> 264

Arg Gln Gln Glu

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Gln Gln Glu Gln

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Gln Glu Gln Ser
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Glu Gln Ser Arg
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Ile Gln Lys Gln
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Phe Ser Ile Arg
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Ser Ile Arg Ser
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Ile Arg Ser Ile
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<210> 272
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Arg Ser Ile Ser
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Ser Ile Ser Gln
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Ile Ser Gln Asn

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Ser Gln Asn Gly

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Gln Asn Gly Tyr

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Tyr Asp Pro Arg

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Asp Pro Arg Gln

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Pro Arg Gln Asn

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Arg Gln Asn Leu

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Leu Asn Asp Val

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Asn Asp Val Leu

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Asp Val Leu Leu

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Val Leu Leu Leu

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Leu Leu Leu Gln

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Arg Glu Ala Arg

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Glu Ala Arg Leu
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Ala Arg Leu Thr
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Arg Leu Thr Pro
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Leu Thr Pro Ser
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Thr Pro Ser Val
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<210> 292
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Pro Ser Val Ala
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<210> 293
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Ser Val Ala Leu
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<210> 294
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Val Ala Leu Val
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Ala Leu Val Pro

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<210> 296

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<400> 296

Leu Val Pro Leu

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<210> 297

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Val Pro Leu Pro

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Pro Leu Pro Pro

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Leu Pro Pro Gln
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Pro Pro Gln Asn
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Pro Gln Asn Ala
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Ala Gly Thr Asn
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Gly Thr Asn Cys

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Thr Asn Cys Gln

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Asn Cys Gln Val

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<210> 306

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Gly Trp Gly Thr

1

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Trp Gly Thr Gln

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Gly Thr Gln Arg
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Thr Gln Arg Leu
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Gln Arg Leu Arg
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<210> 311
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Arg Leu Arg Arg
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Leu Arg Arg Leu
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Arg Arg Leu Phe
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<400> 314

Arg Leu Phe Ser
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Leu Phe Ser Arg
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Phe Ser Arg Phe
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<210> 317
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Phe Pro Arg Val
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Pro Arg Val Leu
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Arg Val Leu Asn
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<210> 320
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Val Leu Asn Val
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Leu Asn Val Thr
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<210> 322

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<400> 322

Thr Val Thr Ser
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<210> 323

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<400> 323

Val Thr Ser Asn
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<210> 324

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<400> 324

Thr Ser Asn Pro
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<400> 325

Ser Asn Pro Cys
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<400> 326

Asn Pro Cys Leu
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<400> 327

Pro Cys Leu Pro
1

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<400> 328

Cys Leu Pro Arg
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<210> 329
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<400> 329

Leu Pro Arg Asp
1

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Pro Arg Asp Met
1

<210> 331
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<400> 331

Arg Asp Met Cys
1

<210> 332
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Asp Met Cys Ile
1

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Met Cys Ile Gly
1

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<400> 334

Cys Ile Gly Val
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Ile Gly Val Phe
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Gly Val Phe Ser
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Val Phe Ser Arg

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Phe Ser Arg Arg

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Ser Arg Arg Gly

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Arg Arg Gly Arg

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Gly Arg Ile Ser
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Arg Ile Ser Gln
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Ser Gln Gly Asp

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Arg Gly Thr Pro
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Val Cys Asn Gly
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Cys Asn Gly Leu
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Asn Gly Leu Ala
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Gly Leu Ala Gln

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Leu Ala Gln Gly

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Ala Gln Gly Val

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Gln Gly Val Ala

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Ala Ser Phe Leu

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Ser Phe Leu Arg

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Phe Leu Arg Arg

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Gln Lys Gln Gly

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Arg Arg Arg Phe
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Arg Arg Phe Arg
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Arg Phe Arg Arg
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Phe Arg Arg Ser
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Arg Arg Ser Ser
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Arg Ser Ser Gly
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Ser Ser Gly Phe
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Ser Gly Phe Phe
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Gly Phe Phe Thr
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Lys Gln Gly Arg
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<400> 372

Leu Phe Arg Asn
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<211> 4
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Phe Arg Asn Trp
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<400> 374

Arg Asn Trp Ile
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<210> 375
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Asn Trp Ile Asp
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Trp Ile Asp Ser
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Ile Asp Ser Val
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Asp Ser Val Leu
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Ser Val Leu Asn

1

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Asn Asn Pro Pro

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Gly Gly Arg Arg

1

<210> 382

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Gly Arg Arg Ala

1

<210> 383

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Arg Arg Ala Arg
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Arg Ala Arg Pro
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Ala Arg Pro His
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Arg Pro His Ala
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Pro His Ala Trp
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His Ala Trp Pro
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Ala Trp Pro Phe
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Trp Pro Phe Met
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Pro Phe Met Val
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Phe Met Val Ser
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Met Val Ser Leu
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Val Ser Leu Gln
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Ser Leu Gln Leu
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Leu Gln Leu Arg

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<210> 397

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<223> Peptide fragment: amino acid residues 19-22 of hNLE

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Gln Leu Arg Gly

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Leu Arg Gly Gly

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Arg Gly Gly His

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Phe Cys Gly Ala
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Cys Gly Ala Thr
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Gly Ala Thr Leu

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Ala Thr Leu Ile

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Thr Leu Ile Ala

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Leu Ile Ala Pro

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Ile Ala Pro Asn

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Ala Pro Asn Phe
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Pro Asn Phe Val
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Val Met Ser Ala
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Ala Ala His Cys
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Ala His Cys Val

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His Cys Val Ala

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Cys Val Ala Asn

1

<210> 420

<211> 4

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Val Ala Asn Val

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Ala Asn Val Asn

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Asn Val Asn Val

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Val Asn Val Arg

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Val Arg Ala Val

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Arg Ala Val Arg

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Ala Val Arg Val

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Val Arg Val Val

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Arg Val Val Leu

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<210> 429

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Leu Gly Ala His

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Gly Ala His Asn
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<210> 431
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Ala His Asn Leu
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His Asn Leu Ser
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Leu Ser Arg Arg
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<210> 435
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Ser Arg Arg Glu
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Arg Arg Glu Pro
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Arg Glu Pro Thr
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Glu Pro Thr Arg
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Pro Thr Arg Gln
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Thr Arg Gln Val
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Gln Val Phe Ala
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<223> Peptide fragment: amino acid residues 69-72 of hNLE

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Val Phe Ala Val
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<210> 444

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<223> Peptide fragment: amino acid residues 70-73 of hNLE

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Phe Ala Val Gln
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<223> Peptide fragment: amino acid residues 71-74 of hNLE

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Ala Val Gln Arg
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<210> 446

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<223> Peptide fragment: amino acid residues 72-75 of hNLE

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Val Gln Arg Ile

1

<210> 447
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<400> 447

Gln Arg Ile Phe
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<210> 448
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Arg Ile Phe Glu
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<210> 449
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Ile Phe Glu Asp
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Phe Glu Asp Gly
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<220>
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<400> 451

Glu Asp Gly Tyr
1

<210> 452
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<400> 452

Asp Gly Tyr Asp
1

<210> 453
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Tyr Asp Pro Val
1

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Asp Pro Val Asn
1

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<223> Peptide fragment: amino acid residues 82-84 of hNLE

<400> 455

Pro Val Asn Leu

1

<210> 456

<211> 4

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<400> 456

Val Asn Leu Leu

1

<210> 457

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Asn Leu Leu Asn

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Leu Leu Asn Asp

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Leu Asn Asp Ile

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Asn Asp Ile Val

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Asp Ile Val Ile

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Ile Val Ile Leu

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Val Ile Leu Gln

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Leu Gln Leu Asn

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Thr Ile Asn Pro
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Val Ala Leu Val

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Ala Leu Val Pro

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Met Gly Trp Gly

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Gly Trp Gly Leu

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Trp Gly Leu Leu

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Leu Gly Arg Asn
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Gly Arg Asn Arg

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Arg Asn Arg Gly

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Gln Glu Leu Asn
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Thr Val Val Thr

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Val Thr Ser Leu

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Thr Ser Leu Cys

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Cys Arg Arg Ser

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Arg Arg Ser Asn

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Arg Ile Ser Gln

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Ile Ser Gln Gly

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Ser Gln Gly Asp

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Gln Gly Asp Ser

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Gly Asp Ser Gly

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Asp Ser Gly Thr

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Leu Val Cys Asn

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Cys Asn Gly Leu
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Asn Gly Leu Ile
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Leu Ile His Gly

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Ile His Gly Ile
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Arg Gly Gly Cys

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Gly Gly Cys Ala

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Gly Cys Ala Ser

1

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Cys Ala Ser Gly

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Ala Ser Gly Leu

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<210> 565

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<400> 565

Ser Gly Leu Tyr

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<210> 566

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Gly Leu Tyr Pro

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Leu Tyr Pro Asp

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Tyr Pro Asp Ala

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Pro Asp Ala Phe

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Asp Ala Phe Ala

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Ala Phe Ala Pro

1

<210> 572

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Phe Ala Pro Val

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Ala Pro Val Ala
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Pro Val Ala Gln
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Val Ala Gln Phe
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Ala Gln Phe Val
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Gln Phe Val Asn
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<220>
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<400> 581

Trp Ile Asp Ser

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<211> 4

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 213-216 of hNLE

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<211> 4

<212> PRT

<213> Artificial sequence

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<211> 4

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<211> 4

<212> PRT

<213> Artificial sequence

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<211> 4

<212> PRT

<213> Artificial sequence

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<210> 588

<211> 221

<212> PRT

<213> Sus sp.

<400> 588

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35 40 45Gly Ser Ala Ser Val Val Leu Gly Ala Tyr Asp Leu Arg Gln Gln Glu
50 55 60

Gln Ser Arg Gln Thr Phe Ser Ile Arg Ser Ile Ser Gln Asn Gly Tyr

Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Pro Asn Phe

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Arg Val Val Leu Gly Ala His Asn Leu Ser Arg Arg Glu Pro Thr Arg		
	85	90 95
Gln Val Phe Ala Val Gln Arg Ile Phe Glu Asn Gly Tyr Asp Pro Val		
	100	105 110
Asn Leu Leu Asn Asp Ile Val Ile Leu Gln Leu Asn Gly Ser Ala Thr		
	115	120 125
Ile Asn Ala Asn Val Gln Val Ala Gln Leu Pro Ala Gln Gly Arg Arg		
	130	135 140
Leu Gly Asn Gly Val Gln Cys Leu Ala Met Gly Trp Gly Leu Leu Gly		
145	150	155 160
Arg Asn Arg Gly Ile Ala Ser Val Leu Gln Glu Leu Asn Val Thr Val		
	165	170 175
Val Thr Ser Leu Cys Arg Arg Ser Asn Val Cys Thr Leu Val Arg Gly		
	180	185 190
Arg Gln Ala Gly Val Cys Phe Gly Asp Ser Gly Ser Pro Leu Val Cys		
	195	200 205
Asn Gly Leu Ile His Gly Ile Ala Ser Phe Val Arg Gly Gly Cys Ala		
	210	215 220
Ser Gly Leu Tyr Pro Asp Ala Phe Ala Pro Val Ala Gln Phe Val Asn		
225	230	235 240
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<400> 590

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<211> 660

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<400> 591

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<210> 592

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<212> DNA

<213> Homo sapiens

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ggcctgtacc cggatgcatt tgccccggtg gcacagtttg ttaactggat cgactctatc    660
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<211> 25

<212> PRT

<213> Artificial sequence

<220>

<223> Peptide fragment: amino acid residues 20-44 of pHPB

<400> 593

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<210> 594

<211> 78

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 96-173 of pHPB

<400> 594

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 <212> PRT
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Val Met Thr Ala Ala Ser Cys Phe Arg
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<210> 596
 <211> 25
 <212> PRT
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<220>
 <223> Peptide fragment: amino acid residues 20-44 of hHBP with
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Val Met Thr Ala Ala Ser Cys Phe Arg
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<210> 597
 <211> 25

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 20-44 of hHBP with mutations N20K,A33P,Q44R

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Val	Met	Thr	Ala	Ala	Ser	Cys	Phe	Arg
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<210> 598

<211> 25

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 20-44 of hHBP with mutations N20K,H24P,A33P,Q44R

<400> 598

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Val	Met	Thr	Ala	Ala	Ser	Cys	Phe	Arg
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<212> PRT

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<223> Reversed sequence: amino acid residues 20-44 of pHBP.

<400> 599

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Gly	Ala	Cys	Phe	Pro	Arg	Gly	Gln	Lys
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Val Leu Thr Ala Ala Ser Cys Phe Arg
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<210> 601

<211> 25

<212> PRT

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<223> Peptide fragment: amino acid residues 20-44 of pHBP with mutation R44Q

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<210> 602

<211> 25

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<223> Peptide fragment: amino acid residues 20-44 of pHBP with mutations K20N,R44Q

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Val Leu Thr Ala Ala Ser Cys Phe Gln
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<211> 25

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 20-44 of pHBP with

mutation R34Q

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Val Leu Thr Ala Ala Ser Cys Phe Arg
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<210> 604

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<213> Artificial sequence

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<223> Peptide fragment consisting of amino acid residues 20-44 of human neutrophil elastase

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<210> 605

<211> 25

<212> PRT

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<223> Peptide fragment consisting of amino acid residues 20-44 of murine neutrophil elastase

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<210> 606

<211> 25

<212> PRT

<213> Artificial sequence

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<223> Peptide fragment: amino acid residues 20-44 of A. gambiae EAA01962

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<210> 607

<211> 5

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<223> R1 amino acid sequence (claim 2)

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<211> 5

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<223> R1 amino acid sequence (claim 2)

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<223> R1 amino acid sequence (claim 2)

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<211> 5

<212> PRT

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<223> R19 amino acid sequences (claim 21)

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CORRECTED VERSION

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PCT

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60/404,155 19 August 2002 (19.08.2002) US
PA 2003 00987 27 June 2003 (27.06.2003) DK

(71) Applicant (for all designated States except US):
LEUKOTECH A/S [DK/DK]; Fruebjergvej 3, DK-2100
Copenhagen Ø (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DJURUP, René**
[DK/DK]; Middelvej 23, DK-2820 Gentofte (DK).
FLODGAARD, Hans, Jakob [DK/DK]; Melvillevej 6,
DK-2900 Hellerup (DK). **NORRIS, Kjeld** [DK/DK];
Ahlmanns Alle 34, DK-2900 Hellerup (DK).

(74) Agent: **HØIBERG A/S**; St. Kongensgade 59A, DK-1264
Copenhagen K (DK).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
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MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO
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ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

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(54) Title: BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF HEPARIN-BINDING PROTEIN (HBP)

(57) Abstract: The present invention relates to providing new peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said fragments for the manufacture of a medicament for the treatment of Gram positive and/or Gram negative infections. Thus, the peptides of the inventions can be used for treatment of pneumonia and meningitis. The peptides of the invention may also be advantageously used for the treatment of any pathological condition demanding modulating of inflammatory response and/or a condition involving sepsis and/or, disseminated intravascular coagulation. Among other pathological conditions, which may be regarded for the treatment with the peptides of the invention, are conditions involving cell apoptosis.



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(10) International Publication Number
WO 2004/016653 A3

(51) International Patent Classification⁷: **C07K 14/47**,
2/00, A61K 38/17, 38/02, A61P 31/04

(21) International Application Number:
PCT/DK2003/000542

(22) International Filing Date: 14 August 2003 (14.08.2003)

(25) Filing Language: English

(26) Publication Language: English

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Copenhagen Ø (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DJURUP, René**
[DK/DK]; Middelvej 23, DK-2820 Gentofte (DK).
FLODGAARD, Hans, Jakob [DK/DK]; Melvillevej 6,
DK-2900 Hellerup (DK). **NORRIS, Kjeld** [DK/DK];
Ahlmanns Allé 34, DK-2900 Hellerup (DK).

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Copenhagen K (DK).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GI, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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a patent (Rule 4.17(ii)) for the following designations AE,
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FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
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PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO
patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BACTERICIDAL, ANTI-APOPTOTIC, PRO-INFLAMMATORY AND ANTI-INFLAMMATORY PEPTIDES OF
HEPARIN-BINDING PROTEIN (HBP) OR HUMAN NEUTROPHIL ELASTASE

(57) Abstract: The present invention relates to providing new peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and using said fragments for the manufacture of a medicament for the treatment of Gram positive and/or Gram negative infections. Thus, the peptides of the inventions can be used for treatment of pneumonia and meningitis. The peptides of the invention may also be advantageously used for the treatment of any pathological condition demanding modulating of inflammatory response and/or a condition involving sepsis and/or, disseminated intravascular coagulation. Among other pathological conditions, which may be regarded for the treatment with the peptides of the invention, are conditions involving cell apoptosis.

WO 2004/016653 A3

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/DK 03/00542

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 C07K2/00 A61K38/17 A61K38/02 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, MEDLINE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 6 071 879 A (PEREIRA HELOISE ANNE) 6 June 2000 (2000-06-06) column 6, line 25 - column 7, line 1 column 12, line 40 - line 50 SEQ ID NO 1</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-63,73

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the international search report

29 APR 2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/DK 03/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PEREIRA H A ET AL: "Synthetic bactericidal peptide based on CAP37: a 37-kDa human neutrophil granule-associated cationic antimicrobial protein chemotactic for monocytes." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 15 MAY 1993, vol. 90, no. 10, 15 May 1993 (1993-05-15), pages 4733-4737, XP002275782 ISSN: 0027-8424 cited in the application page 4734, left-hand column, paragraph 3 page 4736, left-hand column, paragraph 2; figure 5 abstract</p>	1-63,73
X	<p>--- US 5 650 392 A (BRACKETT DANIEL J ET AL) 22 July 1997 (1997-07-22) column 11 -column 12 SEQ ID NO 1</p>	1-63,73
X	<p>--- WO 93 19087 A (UNIV EMORY MED) 30 September 1993 (1993-09-30) page 62, line 17 -page 63, line 16 claims 16,25-27 SEQ ID NO 8</p>	1-63, 66-69,73
X	<p>--- D'CRUZ OSMOND J ET AL: "Sperm immobilizing activity of a synthetic bioactive peptide 20-44 of 37-kDa cationic antimicrobial protein (CAP37) of human neutrophils" JOURNAL OF ANDROLOGY, vol. 16, no. 5, 1995, pages 432-440, XP002275783 ISSN: 0196-3635 abstract</p>	1-58,73
A	<p>--- HEINZELMANN M ET AL: "Heparin binding protein (CAP37) differentially modulates endotoxin-induced cytokine production." INTERNATIONAL JOURNAL OF SURGICAL INVESTIGATION. ENGLAND 2001, vol. 2, no. 6, 2001, pages 457-466, XP002275784 ISSN: 1028-5229 see especially "conslusions" in the abstract</p> <p>--- -/--</p>	64,67-69

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/DK 03/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2 May 2002 (2002-05-02) WEINRAUCH YVETTE ET AL: "Neutrophil elastase targets virulence factors of enterobacteria" Database accession no. PREV200200430146 XP002275787 abstract & NATURE (LONDON), vol. 417, no. 6884, 2 May 2002 (2002-05-02), pages 91-94, ISSN: 0028-0836</p>	1-66,73
A	<p>--- TAPPER HANS ET AL: "Secretion of heparin-binding protein from human neutrophils is determined by its localization in azurophilic granules and secretory vesicles" BLOOD, vol. 99, no. 5, 1 March 2002 (2002-03-01), pages 1785-1793, XP002275785 ISSN: 0006-4971 page 1786, left-hand column, paragraph 2</p>	1-73
A	<p>--- MILIND S. SHROTRI ET AL: "Heparin-binding protein decreases apoptosis in human and murine neutrophils" JOURNAL OF SURGICAL RESEARCH, vol. 89, 2000, pages 53-59, XP002275786 ISSN: 0022-4804 abstract "results" and "conclusions". -----</p>	1-69,73

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International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 67, 70
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 67,70

Present claims 67 and 70 relate to an extremely large number of possible peptides. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the peptides claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been focused on those parts of the claims which appear to be supported and disclosed, namely those parts related to the peptides disclosed as SEQ ID NOs 594 (claim 68) and 593 (claim 71) respectively. Thereto, the more general aspects underlying the invention, regarding the use of peptides derived from human HBP and porcine HBP as proinflammatory peptides and anti-inflammatory peptides respectively, have been included in the search.

Regarding claim 68: the definition of SEQ ID NO:594 differs between the sequence listing and the description. The definition of the description has been used in the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-73

The present application has been considered to contain several inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT for the following reasons:

The prior art has been identified as: US6071879 (D1) and Periera et al. "Synthetic bactericidal peptide based on CAP37: A 37-kDa human neutrophil granule-associated cationic antimicrobial protein chemotactic for monocytes, Proceedings of the National Academy of Sciences of the United States of America (1993), 90(10), 4733-7 (D2).

D1 shows the use of a peptide consisting of amino acids 20-44 of CAP37 or effective subunits thereof in the treatment of bacterial infections (activity against gram positive and gram negative bacteria) and septic shock. See SEQ ID NO: 1, col. 6 line 25-col. 7 line 1 and col. 12 lines 40-50.

D2 shows that peptides consisting of amino acids 20-44 of CAP37 or human neutrophil elastase (ELAS) have bactericidal effect. The CAP37-derived peptide shows effect against gram positive as well as gram negative bacteria. See abstract, p. 4734 left column paragraph 3, p. 4736 fig. 5 and left column paragraph 2.

2. Claims: -

Thus, within the group of peptides covered by claims 1-52, previously known peptides are included. The use of such peptides in treatment of bacterial infections or sepsis is also disclosed in prior art.

The special technical feature of each of the peptides that makes a contribution over prior art (Rule 13.2 PCT) is the specific sequence of the peptide. From this special technical feature the objective problem to be solved by this and all further inventions is to provide alternative peptides. Therefore, each of the claimed peptides constitutes one invention.

However, if a group of peptides share the same function (e.g. that they function as proinflammatory peptides or that they function as anti-inflammatory peptides or can be used for the prevention of cell apoptosis), and if this function constitutes a special technical features which make a contribution over the prior art (Rule 13.2 PCT), such peptides can possibly be grouped as one invention according to their use/function. So far, however, no obvious grouping of the peptides could be made given the information disclosed in the description. It is not evident from the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

description which sequence has which function, and therefore the peptides could not be grouped in a logic way. For example, not all peptides covered by claims 1-53 can be used to inhibit inflammatory response. Thus, so far each of the sequences covered by present claims 1-52 is considered to represent one invention.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal

Application No

PCT/DK 03/00542

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6071879	A	06-06-2000	US 5877151 A	02-03-1999
			US 5627262 A	06-05-1997
			US 5607916 A	04-03-1997
			US 5458874 A	17-10-1995
			US 5484885 A	16-01-1996
			US 5650392 A	22-07-1997
			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			AU 6033690 A	06-02-1991
			WO 9100907 A1	24-01-1991

US 5650392	A	22-07-1997	US 5607916 A	04-03-1997
			US 5458874 A	17-10-1995
			US 5484885 A	16-01-1996
			US 6071879 A	06-06-2000
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			US 5877151 A	02-03-1999
			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			AU 6033690 A	06-02-1991
			WO 9100907 A1	24-01-1991

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			AU 4808993 A	21-10-1993
			WO 9319087 A1	30-09-1993
			US 5607916 A	04-03-1997
			US 6071879 A	06-06-2000
			US 5650392 A	22-07-1997
			US 5627262 A	06-05-1997
			US 5877151 A	02-03-1999
			US 5458874 A	17-10-1995
